



## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification <sup>6</sup> : C12N 15/11, 15/63, 15/00, 15/12, A61K 38/17, C07K 16/00, C12P 21/02, C12Q 1/68, G01N 33/68		A1	(11) International Publication Number: WO 99/03990 (43) International Publication Date: 28 January 1999 (28.01.99)
(21) International Application Number: PCT/US98/14613 (22) International Filing Date: 15 July 1998 (15.07.98)		(71) Applicant (for all designated States except US): HUMAN GENOME SCIENCES, INC. [US/US]; 9410 Key West Avenue, Rockville, MD 20850 (US). (72) Inventors; and (75) Inventors/Applicants (for US only): RUBEN, Steven, M. [US/US]; 18528 Heritage Hills Drive, Olney, MD 20832 (US). ROSEN, Craig, A. [US/US]; 22400 Rolling Hill Road, Laytonsville, MD 20882 (US). YOUNG, Paul, E. [US/US]; 122 Beckwith Street, Gaithersburg, MD 20878 (US). GREENE, John, M. [US/US]; 872 Diamond Drive, Gaithersburg, MD 20878 (US). NI, Jian [CN/US]; 5502 Manorfield Road, Rockville, MD 20853 (US). FENG, Ping [CN/US]; 4 Relda Court, Gaithersburg, MD 20878 (US). FLORENCE, Kimberly, A. [US/US]; 12805 Atlantic Av- enue, Rockville, MD 20851 (US). HU, Jing-Shan [CN/US]; 1247 Lakeside Drive #3034, Sunnysvale, CA 94086 (US). FERRIE, Ann, M. [US/US]; 13203 L. Astoria Hill Court, Germantown, MD 20874 (US). YU, Guo-Liang [CN/US]; 1714C Marina Court, San Mateo, CA 94403 (US). DUAN, Roxanne [US/US]; 5515 Northfield Road, Bethesda, MD 20817 (US). FOUAD, Janet [SY/US]; #202, 140 High Street, Westerly, RI 02891 (US). (74) Agents: BROOKES, A., Anders et al.; Human Genome Sciences, Inc., 9410 Key West Avenue, Rockville, MD 20850 (US). (81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).	
(30) Priority Data:			
60/052,661	16 July 1997 (16.07.97)	US	
60/052,872	16 July 1997 (16.07.97)	US	
60/052,871	16 July 1997 (16.07.97)	US	
60/052,874	16 July 1997 (16.07.97)	US	
60/052,873	16 July 1997 (16.07.97)	US	
60/052,870	16 July 1997 (16.07.97)	US	
60/052,875	16 July 1997 (16.07.97)	US	
60/053,440	22 July 1997 (22.07.97)	US	
60/053,441	22 July 1997 (22.07.97)	US	
60/053,442	22 July 1997 (22.07.97)	US	
60/055,726	18 August 1997 (18.08.97)	US	
60/055,724	18 August 1997 (18.08.97)	US	
60/056,359	18 August 1997 (18.08.97)	US	
60/055,725	18 August 1997 (18.08.97)	US	
60/055,985	18 August 1997 (18.08.97)	US	
60/055,952	18 August 1997 (18.08.97)	US	
60/055,946	18 August 1997 (18.08.97)	US	
60/055,683	18 August 1997 (18.08.97)	US	
60/055,989	18 August 1997 (18.08.97)	US	
60/056,361	18 August 1997 (18.08.97)	US	
		Published With international search report.	
(54) Title: 64 HUMAN SECRETED PROTEINS			
(57) Abstract			
<p>The present invention relates to 64 novel human secreted proteins and isolated nucleic acids containing the coding regions of the genes encoding such proteins. Also provided are vectors, host cells, antibodies, and recombinant methods for producing human secreted proteins. The invention further relates to diagnostic and therapeutic methods useful for diagnosing and treating disorders related to these novel human secreted proteins.</p>			

*FOR THE PURPOSES OF INFORMATION ONLY*

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Larvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece			TR	Turkey
BG	Bulgaria	HU	Hungary	ML	Mali	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MN	Mongolia	UA	Ukraine
BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda
BY	Belarus	IS	Iceland	MW	Malawi	US	United States of America
CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	NZ	New Zealand		
CM	Cameroon	KR	Republic of Korea	PL	Poland		
CN	China	KZ	Kazakstan	PT	Portugal		
CU	Cuba	LC	Saint Lucia	RO	Romania		
CZ	Czech Republic	LI	Liechtenstein	RU	Russian Federation		
DE	Germany	LK	Sri Lanka	SD	Sudan		
DK	Denmark	LR	Liberia	SE	Sweden		
EE	Estonia			SG	Singapore		

## 64 Human Secreted Proteins

### *Field of the Invention*

This invention relates to newly identified polynucleotides and the polypeptides encoded by these polynucleotides, uses of such polynucleotides and polypeptides, and  
5 their production.

### *Background of the Invention*

Unlike bacterium, which exist as a single compartment surrounded by a membrane, human cells and other eucaryotes are subdivided by membranes into many functionally distinct compartments. Each membrane-bounded compartment, or  
10 organelle, contains different proteins essential for the function of the organelle. The cell uses "sorting signals," which are amino acid motifs located within the protein, to target proteins to particular cellular organelles.

One type of sorting signal, called a signal sequence, a signal peptide, or a leader sequence, directs a class of proteins to an organelle called the endoplasmic reticulum  
15 (ER). The ER separates the membrane-bounded proteins from all other types of proteins. Once localized to the ER, both groups of proteins can be further directed to another organelle called the Golgi apparatus. Here, the Golgi distributes the proteins to vesicles, including secretory vesicles, the cell membrane, lysosomes, and the other organelles.

20 Proteins targeted to the ER by a signal sequence can be released into the extracellular space as a secreted protein. For example, vesicles containing secreted proteins can fuse with the cell membrane and release their contents into the extracellular space - a process called exocytosis. Exocytosis can occur constitutively or after receipt of a triggering signal. In the latter case, the proteins are stored in secretory vesicles (or  
25 secretory granules) until exocytosis is triggered. Similarly, proteins residing on the cell membrane can also be secreted into the extracellular space by proteolytic cleavage of a "linker" holding the protein to the membrane.

Despite the great progress made in recent years, only a small number of genes encoding human secreted proteins have been identified. These secreted proteins include  
30 the commercially valuable human insulin, interferon, Factor VIII, human growth hormone, tissue plasminogen activator, and erythropoietin. Thus, in light of the pervasive role of secreted proteins in human physiology, a need exists for identifying and characterizing novel human secreted proteins and the genes that encode them. This knowledge will allow one to detect, to treat, and to prevent medical disorders by using  
35 secreted proteins or the genes that encode them.

### *Summary of the Invention*

The present invention relates to novel polynucleotides and the encoded polypeptides. Moreover, the present invention relates to vectors, host cells, antibodies, and recombinant methods for producing the polypeptides and polynucleotides. Also provided are diagnostic methods for detecting disorders related to the polypeptides, and therapeutic methods for treating such disorders. The invention further relates to screening methods for identifying binding partners of the polypeptides.

### *Detailed Description*

#### **Definitions**

The following definitions are provided to facilitate understanding of certain terms used throughout this specification.

In the present invention, "isolated" refers to material removed from its original environment (e.g., the natural environment if it is naturally occurring), and thus is altered "by the hand of man" from its natural state. For example, an isolated polynucleotide could be part of a vector or a composition of matter, or could be contained within a cell, and still be "isolated" because that vector, composition of matter, or particular cell is not the original environment of the polynucleotide.

In the present invention, a "secreted" protein refers to those proteins capable of being directed to the ER, secretory vesicles, or the extracellular space as a result of a signal sequence, as well as those proteins released into the extracellular space without necessarily containing a signal sequence. If the secreted protein is released into the extracellular space, the secreted protein can undergo extracellular processing to produce a "mature" protein. Release into the extracellular space can occur by many mechanisms, including exocytosis and proteolytic cleavage.

As used herein, a "polynucleotide" refers to a molecule having a nucleic acid sequence contained in SEQ ID NO:X or the cDNA contained within the clone deposited with the ATCC. For example, the polynucleotide can contain the nucleotide sequence of the full length cDNA sequence, including the 5' and 3' untranslated sequences, the coding region, with or without the signal sequence, the secreted protein coding region, as well as fragments, epitopes, domains, and variants of the nucleic acid sequence. Moreover, as used herein, a "polypeptide" refers to a molecule having the translated amino acid sequence generated from the polynucleotide as broadly defined.

In the present invention, the full length sequence identified as SEQ ID NO:X was often generated by overlapping sequences contained in multiple clones (contig



analysis). A representative clone containing all or most of the sequence for SEQ ID NO:X was deposited with the American Type Culture Collection ("ATCC"). As shown in Table 1, each clone is identified by a cDNA Clone ID (Identifier) and the ATCC Deposit Number. The ATCC is located at 10801 University Boulevard,  
5 Manassas, Virginia 20110-2209, USA. The ATCC deposit was made pursuant to the terms of the Budapest Treaty on the international recognition of the deposit of microorganisms for purposes of patent procedure.

A "polynucleotide" of the present invention also includes those polynucleotides capable of hybridizing, under stringent hybridization conditions, to sequences contained  
10 in SEQ ID NO:X, the complement thereof, or the cDNA within the clone deposited with the ATCC. "Stringent hybridization conditions" refers to an overnight incubation at 42°C in a solution comprising 50% formamide, 5x SSC (750 mM NaCl, 75 mM sodium citrate), 50 mM sodium phosphate (pH 7.6), 5x Denhardt's solution, 10% dextran sulfate, and 20 µg/ml denatured, sheared salmon sperm DNA, followed by washing the  
15 filters in 0.1x SSC at about 65°C.

Also contemplated are nucleic acid molecules that hybridize to the polynucleotides of the present invention at lower stringency hybridization conditions. Changes in the stringency of hybridization and signal detection are primarily accomplished through the manipulation of formamide concentration (lower percentages  
20 of formamide result in lowered stringency); salt conditions, or temperature. For example, lower stringency conditions include an overnight incubation at 37°C in a solution comprising 6X SSPE (20X SSPE = 3M NaCl; 0.2M NaH<sub>2</sub>PO<sub>4</sub>; 0.02M EDTA, pH 7.4), 0.5% SDS, 30% formamide, 100 µg/ml salmon sperm blocking DNA; followed by washes at 50°C with 1XSSPE, 0.1% SDS. In addition, to achieve even  
25 lower stringency, washes performed following stringent hybridization can be done at higher salt concentrations (e.g. 5X SSC).

Note that variations in the above conditions may be accomplished through the inclusion and/or substitution of alternate blocking reagents used to suppress background in hybridization experiments. Typical blocking reagents include  
30 Denhardt's reagent, BLOTTO, heparin, denatured salmon sperm DNA, and commercially available proprietary formulations. The inclusion of specific blocking reagents may require modification of the hybridization conditions described above, due to problems with compatibility.

Of course, a polynucleotide which hybridizes only to polyA+ sequences (such  
35 as any 3' terminal polyA+ tract of a cDNA shown in the sequence listing), or to a

complementary stretch of T (or U) residues, would not be included in the definition of "polynucleotide," since such a polynucleotide would hybridize to any nucleic acid molecule containing a poly (A) stretch or the complement thereof (e.g., practically any double-stranded cDNA clone).

5           The polynucleotide of the present invention can be composed of any polyribonucleotide or polydeoxribonucleotide, which may be unmodified RNA or DNA or modified RNA or DNA. For example, polynucleotides can be composed of single- and double-stranded DNA, DNA that is a mixture of single- and double-stranded regions, single- and double-stranded RNA, and RNA that is mixture of single- and  
10       double-stranded regions, hybrid molecules comprising DNA and RNA that may be single-stranded or, more typically, double-stranded or a mixture of single- and double-stranded regions. In addition, the polynucleotide can be composed of triple-stranded regions comprising RNA or DNA or both RNA and DNA. A polynucleotide may also contain one or more modified bases or DNA or RNA backbones modified for stability  
15       or for other reasons. "Modified" bases include, for example, tritylated bases and unusual bases such as inosine. A variety of modifications can be made to DNA and RNA; thus, "polynucleotide" embraces chemically, enzymatically, or metabolically modified forms.

          The polypeptide of the present invention can be composed of amino acids joined  
20       to each other by peptide bonds or modified peptide bonds, i.e., peptide isosteres, and may contain amino acids other than the 20 gene-encoded amino acids. The polypeptides may be modified by either natural processes, such as posttranslational processing, or by chemical modification techniques which are well known in the art. Such modifications are well described in basic texts and in more detailed monographs,  
25       as well as in a voluminous research literature. Modifications can occur anywhere in a polypeptide, including the peptide backbone, the amino acid side-chains and the amino or carboxyl termini. It will be appreciated that the same type of modification may be present in the same or varying degrees at several sites in a given polypeptide. Also, a given polypeptide may contain many types of modifications. Polypeptides may be  
30       branched, for example, as a result of ubiquitination, and they may be cyclic, with or without branching. Cyclic, branched, and branched cyclic polypeptides may result from posttranslation natural processes or may be made by synthetic methods. Modifications include acetylation, acylation, ADP-ribosylation, amidation, covalent attachment of flavin, covalent attachment of a heme moiety, covalent attachment of a  
35       nucleotide or nucleotide derivative, covalent attachment of a lipid or lipid derivative, covalent attachment of phosphatidylinositol, cross-linking, cyclization, disulfide bond formation, demethylation, formation of covalent cross-links, formation of cysteine,

formation of pyroglutamate, formylation, gamma-carboxylation, glycosylation, GPI anchor formation, hydroxylation, iodination, methylation, myristoylation, oxidation, pegylation, proteolytic processing, phosphorylation, prenylation, racemization, selenoylation, sulfation, transfer-RNA mediated addition of amino acids to proteins such as arginylation, and ubiquitination. (See, for instance, PROTEINS - STRUCTURE AND MOLECULAR PROPERTIES, 2nd Ed., T. E. Creighton, W. H. Freeman and Company, New York (1993); POSTTRANSLATIONAL COVALENT MODIFICATION OF PROTEINS, B. C. Johnson, Ed., Academic Press, New York, pgs. 1-12 (1983); Seifter et al., Meth Enzymol 182:626-646 (1990); Rattan et al., Ann NY Acad Sci 663:48-62 (1992).)

"SEQ ID NO:X" refers to a polynucleotide sequence while "SEQ ID NO:Y" refers to a polypeptide sequence, both sequences identified by an integer specified in Table 1.

"A polypeptide having biological activity" refers to polypeptides exhibiting activity similar, but not necessarily identical to, an activity of a polypeptide of the present invention, including mature forms, as measured in a particular biological assay, with or without dose dependency. In the case where dose dependency does exist, it need not be identical to that of the polypeptide, but rather substantially similar to the dose-dependence in a given activity as compared to the polypeptide of the present invention (i.e., the candidate polypeptide will exhibit greater activity or not more than about 25-fold less and, preferably, not more than about tenfold less activity, and most preferably, not more than about three-fold less activity relative to the polypeptide of the present invention.)

## **Polynucleotides and Polypeptides of the Invention**

### **FEATURES OF PROTEIN ENCODED BY GENE NO: 1**

Preferred polypeptides encoded by this gene comprise the following amino acid sequence:

IRHELGCSWRFRAVKAASAQGLFLSAPGPAARRCHGVVRCFSTCRALTA  
RCTGRVPWEACLYSSEPPLTETVARSVSWTCELALTCYAPRALSGAPVLCRHD  
V (SEQ ID NO:155). Also provided are polynucleotides encoding such polypeptides.

This gene is expressed in human substantia nigra tissue.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are

not limited to, neurological disorders or abnormalities. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the neurological systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., brain and of the tissue of the nervous system, and cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO:83 as residues: Pro-30 to Leu-35.

The tissue distribution indicates that the protein products of this gene are useful for diagnosis and treatment of neurological disorders and abnormalities. Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:11 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 544 of SEQ ID NO:11, b is an integer of 15 to 558, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:11, and where the b is greater than or equal to a + 14.

## 25 FEATURES OF PROTEIN ENCODED BY GENE NO: 2

This gene is expressed primarily in breast and testes.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, tumors, particularly those of the breast or testes. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the breast and testes, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., reproductive tissue, and cancerous and wounded tissues) or bodily fluids (e.g., breast milk, seminal fluid, serum, plasma, urine, synovial fluid and

spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO:84 as residues:

5 Ser-32 to His-37.

The tissue distribution indicates that the protein products of this gene are useful for diagnosis and treatment of disorders or abnormalities of breast and testes such as tumors of those tissues. Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:12 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 701 of SEQ ID NO:12, b is an integer of 15 to 715, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:12, and where the b is greater than or equal to a + 14.

### FEATURES OF PROTEIN ENCODED BY GENE NO: 3

20 This gene is expressed in apoptotic T cells.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, disorder or abnormalities of T cells. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., cells and tissues of the immune system, developmental tissue, and cancerous and wounded tissues) or bodily fluids (e.g., lymph seminal fluid, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO:85 as residues: Met-1 to Glu-6, Leu-39 to Lys-46.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for diagnosis and treatment of disorders in T cells and other immune system disorders such as inflammation. Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:13 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 824 of SEQ ID NO:13, b is an integer of 15 to 838, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:13, and where the b is greater than or equal to a + 14.

#### 15 **FEATURES OF PROTEIN ENCODED BY GENE NO: 4**

The translation product of this gene shares sequence homology with ubiquitin-conjugating enzyme (UCE) involved in selective protein degradation. Based on the sequence similarity, the translation product of this gene is expected to share biological activities with UCE proteins. Such activities are known in the art and described elsewhere herein. Preferred polypeptides encoded by this gene comprise the following amino acid sequence:

FLAIHFPTDFPLKPPKVAFTRMYFPNSNSNGSTCLDILWSQWSPAL (SEQ ID NO: 156). Also provided are polynucleotides encoding such polypeptides.

This gene is expressed primarily in testes.

25 Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, disorders in testes, particularly cell cycle disorders, (e.g. testes tumor). Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the testes and reproductive systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., reproductive tissues, and cancerous and wounded tissues) or bodily fluids (e.g., seminal fluid, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene

expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution and homology to ubiquitin-conjugating enzyme indicates that the protein product of this gene is useful for diagnosis and treatment of disorders in testes and reproductive system such as tumors, as well as the treatment of tumors of other origins. Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:14 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 499 of SEQ ID NO:14, b is an integer of 15 to 513, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:14, and where the b is greater than or equal to a + 14.

#### FEATURES OF PROTEIN ENCODED BY GENE NO: 5

This gene is expressed primarily in testes.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, disorders and abnormalities in the testes. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the reproductive system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., reproductive tissue, and cancerous and wounded tissues) or bodily fluids (e.g., seminal fluid, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, (i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder). Preferred epitopes include those comprising a sequence shown in SEQ ID NO:87 as residues: Ser-22 to Thr-32, Pro-37 to Ser-42.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for diagnosis and treatment of disorders in testes and the reproductive system. Many polynucleotide sequences, such as EST sequences,

are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:15 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 698 of SEQ ID NO:15, b is an integer of 15 to 712, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:15, and where the b is greater than or equal to a + 14.

#### FEATURES OF PROTEIN ENCODED BY GENE NO: 6

This gene is expressed primarily in thymus, activated monocytes and spleen.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a

biological sample and for diagnosis of diseases and conditions which include, but are not limited to, disorders and abnormalities of immune function and hematopoiesis, e.g. leukemia. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune and hematopoietic systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., endocrine tissue cell and tissue of the immune system, and haematopoietic tissue, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution indicates that the protein products of this gene are useful for diagnosis and treatment of immunological and hematopoietic disorders such as leukemia. Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:16 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more

polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 638 of SEQ ID NO:16, b is an integer of 15 to



652, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:16, and where the b is greater than or equal to a + 14.

#### FEATURES OF PROTEIN ENCODED BY GENE NO: 7

5 This gene is expressed in T cells.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, T cell dysfunction. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., cells and tissue of the immune system, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for diagnosis and treatment of disorders in T cells and immune systems. Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:17 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 728 of SEQ ID NO:17, b is an integer of 15 to 742, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:17, and where the b is greater than or equal to a + 14.

#### FEATURES OF PROTEIN ENCODED BY GENE NO: 8

This gene is expressed primarily in pleural cancer and to a less extent in T cells.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are

not limited to, pleural cancer. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the pleural system, expression of this gene at  
5 significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., cells and tissue of the immune system, pleural tissue and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in  
10 healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO:90 as residues: Ser-30 to Tyr-37.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for diagnosis and treatment of pleural cancer.  
15 Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:18 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome.  
20 Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1205 of SEQ ID NO:18, b is an integer of 15 to 1219, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:18, and where the b is greater than or equal to a + 14.

25

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 9**

This gene is expressed in endothelial cells that shares the same origin as hematopoietic cells and in spleen and liver which are hematopoietic tissues.

Therefore, polynucleotides and polypeptides of the invention are useful as  
30 reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, disorders of endothelial cells or hematopoiesis. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of  
35 disorders of the above tissues or cells, particularly of the endothelial and hematopoietic systems, expression of this gene at significantly higher or lower levels may be routinely

detected in certain tissues or cell types (e.g., endothelial tissue, haematopoietic cells and tissue, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and treatment of disorders in endothelial or hematopoietic systems. Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:19 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 860 of SEQ ID NO:19, b is an integer of 15 to 874, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:19, and where the b is greater than or equal to a + 14.

## 20 FEATURES OF PROTEIN ENCODED BY GENE NO: 10

This gene is expressed primarily in breast lymph node and to a lesser extent in melanocytes.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, metastatic melanoma. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the lymphatic system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., reproductive tissue, cells and tissue of the immune system, cancerous and wounded tissues) or bodily fluids (e.g., lymph, breast milk, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution of this gene in melanocytes and lymph node indicates that the protein product of this gene is useful for the diagnosis and treatment of metastatic melanoma involving lymphatic tissues. Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:20 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 450 of SEQ ID NO:20, b is an integer of 15 to 464, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:20, and where the b is greater than or equal to a + 14.

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 11**

This gene is believed to reside on chromosome 2. Therefore, this gene is useful in linkage analysis as a marker for chromosome 2.

This gene is expressed primarily in infant brain and to a lesser extent in fetal liver/spleen.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, neurological disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the central nervous system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., neural tissue, cells and tissue of the immune system, developing tissue, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, amniotic fluid, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level; (i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder). Preferred epitopes include those comprising a sequence shown in SEQ ID NO:93 as residues: Tyr-59 to Gln-68, His-84 to Leu-90, Ser-105 to Asn-110, Leu-112 to Pro-118.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for diagnosis and treatment of neurological

disorders. Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:21 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 623 of SEQ ID NO:21, b is an integer of 15 to 637, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:21, and where the b is greater than or equal to a + 14.

#### FEATURES OF PROTEIN ENCODED BY GENE NO: 12

This gene is expressed primarily in adipose tissue.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, metabolic disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the endocrine system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., adipose tissue, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for regulation of fat metabolism and treatment of obesity. Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:22 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 738 of SEQ ID NO:22, b is an integer of 15 to

752, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:22, and where the b is greater than or equal to a + 14.

### FEATURES OF PROTEIN ENCODED BY GENE NO: 13

5       The translation product of this gene shares sequence homology with NADH:ubiquinone oxidoreductase, the first enzyme in the respiratory electron transport chain of mitochondria.

      This gene is expressed primarily in HSC172 cells and to a lesser extent in pineal gland.

10       Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, jet lag. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential  
15       identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the endocrine system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., endocrine tissue, metabolic tissue, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or  
20       another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO:95 as residues: Thr-30 to Val-38, Glu-49 to Ile-54.

25       The tissue distribution and homology to NADH:ubiquinone oxidoreductase indicates that polynucleotides and polypeptides corresponding to this gene are useful for minimizing the negative effects of travel across time zones by altering the body's circadian clock. Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are  
30       related to SEQ ID NO:23 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of  
35       a-b, where a is any integer between 1 to 478 of SEQ ID NO:23, b is an integer of 15 to

492, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:23, and where the b is greater than or equal to a + 14.

#### FEATURES OF PROTEIN ENCODED BY GENE NO: 14

5 This gene is expressed primarily in synovial IL-1/TNF stimulated cells.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, arthritis. Similarly, polypeptides and antibodies directed to these  
10 polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the skeletal system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., skeletal tissue and cancerous and wounded tissues) or bodily fluids (e.g.,  
15 lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution indicates that polynucleotides and polypeptides  
20 corresponding to this gene are useful for treatment of degenerative conditions of joints, including arthritis. Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:24 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically  
25 excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 518 of SEQ ID NO:24, b is an integer of 15 to 532, where both a and b correspond to the positions of nucleotide  
30 residues shown in SEQ ID NO:24, and where the b is greater than or equal to a + 14.

#### FEATURES OF PROTEIN ENCODED BY GENE NO: 15

This gene is expressed primarily in 12 Week Old Early Stage Human.

Therefore, polynucleotides and polypeptides of the invention are useful as  
35 reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are

not limited to, developmental disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the fetal systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g.,  
5 developing tissue, and cancerous and wounded tissues) or bodily fluids (e.g., amniotic fluid, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an  
10 individual not having the disorder.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for diagnosis and treatment of some developmental disorders. Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences  
15 are related to SEQ ID NO:25 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general  
20 formula of a-b, where a is any integer between 1 to 906 of SEQ ID NO:25, b is an integer of 15 to 920, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:25, and where the b is greater than or equal to a + 14.

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 16**

25 This gene is expressed primarily in thymus and to a lesser extent in neutrophils.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, immune disorders. Similarly, polypeptides and antibodies directed to  
30 these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., cells and tissue of the immune system, and cancerous and wounded  
35 tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder,



relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for diagnosis and treatment of some immune disorders including lupus and other disorders involving thymic dysfunction. Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:26 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 903 of SEQ ID NO:26, b is an integer of 15 to 917, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:26, and where the b is greater than or equal to a + 14.

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 17**

This gene is expressed primarily in fibrosarcoma and to a lesser extent in IL1 and IPS induced neutrophils.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, fibrosarcoma. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., connective tissue, and cells and tissue of the immune system, and cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO:99 as residues: Gly-6 to Pro-11.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for diagnosis and treatment of fibrosarcoma or

other immune disorders. Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:27 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically  
5 excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 648 of SEQ ID NO:27, b is an integer of 15 to 662, where both a and b correspond to the positions of nucleotide  
10 residues shown in SEQ ID NO:27, and where the b is greater than or equal to a + 14.

### FEATURES OF PROTEIN ENCODED BY GENE NO: 18

Preferred polypeptides comprise the following amino acid sequence:  
MLLTPHFNVANPQNLLAGLWLENEHSFTLMAPERARTHHCQPEERKVLFCFLFP  
15 IVPNSQAQVQPPQMPPFCCAAAKEKTQEEQLQEPLGSQCPDTCPNSLC (SEQ ID NO: 157). Polynucleotides encoding such polypeptides are also provided.

This gene is expressed primarily in jurkat T-Cells in S phase, and to a lesser extent in IL-1 and LPS induced neutrophils.

Therefore, polynucleotides and polypeptides of the invention are useful as  
20 reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, immune disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above  
25 tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., cells and tissue of the immune system, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative  
30 to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO:100 as residues: Lys-97 to Gln-106, Gln-112 to Pro-118, Pro-123 to Lys-130, Arg-153 to Gly-158.

The tissue distribution indicates that polynucleotides and polypeptides  
35 corresponding to this gene are useful for diagnosis and treatment of immune disorders related to jurkat T-cells and induced neutrophils. Many polynucleotide sequences, such

as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:28 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To  
5 list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 685 of SEQ ID NO:28, b is an integer of 15 to 699, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:28, and where the b is greater  
10 than or equal to a + 14.

#### FEATURES OF PROTEIN ENCODED BY GENE NO: 19

The translation product of this gene shares sequence homology with FK506-binding protein FKBP-12 and FKBP13, members of a family of proteins which bind  
15 the immunosuppressant drugs FK506 and rapamycin. The homology to FK506 binding proteins indicates that the protein encoded by this gene has similar activity to the known FK506 BP family members. Such activity may be assayed according to methods known in the art and described elsewhere herein. Preferred polypeptides encoded by this gene comprise the following amino acid sequence:

20 MRLFLWNAVLTLFVTSLLIGALIPPEVK  
IEVLQKPFICHRKTKGGDLMLVHYEGYLEKDGSLEHSTHKNNGQPIWFTLGI  
LEALKGWDQGLKGMVCGEKRKLIIPPALGYGKEGKGKIPPESTLIFNIDLLEIR  
NGPRSHESFQEMDLNDDWKLSKDEVKAYLKKEFEKHGAVVNESHHDALVEDI  
FDKEDEDKDGFISAREFTYKHDEL (SEQ ID NO: 158) or comprise a mature form

25 of the foregoing polypeptide having the following amino acid sequence:  
EVKIEVLQKPFICHRKTKGGDLMLVHYEGYLEKDGSLEHSTHKNNGQPIWF  
TLGILEALKGWDQGLKGMVCGEKRKLIIPPALGYGKEGKGKIPPESTLIFNIDL  
LEIRNGPRSHESFQEMDLNDDWKLSKDEVKAYLKKEFEKHGAVVNESHHDAL  
VEDIFDKEDEDKDGFISAREFTYKHDEL (SEQ ID NO: 159). . Polynucleotides  
30 encoding these polypeptides are also provided. Particularly preferred is the following polynucleotide sequence:

ATGAGGCTTTTCTTGTGGAACGCGGTCTTGACTCTGTTTCGTCACTTCT  
TTGATTGGGGCTTTGATCCCTGAACCAGAAGTGAAAATTGAAGTTCTCCAGA  
AGCCATTCATCTGCCATCGCAAGACCAAAGGAGGGGATTTGATGTTGGTCC  
35 ACTATGAAGGCTACTTAGAAAAGGACGGCTCCTTATTTCACTCCACTCACAA  
ACATAACAATGGTCAGCCCATTGTTTACCCTGGGCATCCTGGAGGCTCTC

AAAGGTTGGGACCAGGGCTTGAAAGGAATGTGTGTAGGAGAGAAGAGAAA  
 GCTCATCATTCCTCCTGCTCTGGGCTATGGAAAAGAAGGAAAAGGTAAAATT  
 CCCCCAGAAAGTACACTGATATTTAATATTGATCTCCTGGAGATTTCGAAATG  
 GACCAAGATCCCATGAATCATTCCAAGAAATGGATCTTAATGATGACTGGAA  
 5 ACTCTCTAAAGATGAGGTTAAAGCATATTTAAAGAAGGAGTTTGAAAAACAT  
 GGTGCGGTGGTGAATGAAAGTCATCATGATGCTTTGGTGGAGGATATTTTT  
 GATAAAGAAGATGAAGACAAAGATGGGTTTATATCTGCCAGAGAATTTACAT  
 ATAAACACGATGAG TTA (SEQ ID NO:160), and the portion of it, nucleotide  
 residues 76 to the 3' end, which encode the mature form shown above.

10 This gene is expressed primarily in fetal heart, ovary, and thymus.

Therefore, polynucleotides and polypeptides of the invention are useful as  
 reagents for differential identification of the tissue(s) or cell type(s) present in a  
 biological sample and for diagnosis of diseases and conditions which include, but are  
 not limited to, immune dysfunction such as autoimmune disorders. Similarly,  
 15 polypeptides and antibodies directed to these polypeptides are useful in providing  
 immunological probes for differential identification of the tissue(s) or cell type(s). For  
 a number of disorders of the above tissues or cells, particularly of the immune system,  
 expression of this gene at significantly higher or lower levels may be routinely detected  
 in certain tissues or cell types (e.g., cells and tissue of the immune system, and  
 20 cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine,  
 synovial fluid and spinal fluid) or another tissue or cell sample taken from an  
 individual having such a disorder, relative to the standard gene expression level, i.e.,  
 the expression level in healthy tissue or bodily fluid from an individual not having the  
 disorder.

25 The tissue distribution and homology to FK506-binding protein FKBP-12 and  
 FKBP13 indicates that polynucleotides and polypeptides corresponding to this gene are  
 useful for identifying immunosuppressant drugs, and may be used in combination with  
 immunosuppressant drugs for therapeutic purposes in the treatment of autoimmune  
 diseases and organ/tissue transplant rejection. Many polynucleotide sequences, such as  
 30 EST sequences, are publicly available and accessible through sequence databases.  
 Some of these sequences are related to SEQ ID NO:29 and may have been publicly  
 available prior to conception of the present invention. Preferably, such related  
 polynucleotides are specifically excluded from the scope of the present invention. To  
 list every related sequence is cumbersome. Accordingly, preferably excluded from the  
 35 present invention are one or more polynucleotides comprising a nucleotide sequence  
 described by the general formula of a-b, where a is any integer between 1 to 1623 of

SEQ ID NO:29, b is an integer of 15 to 1637, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:29, and where the b is greater than or equal to a + 14.

## 5 FEATURES OF PROTEIN ENCODED BY GENE NO: 20

The protein product of this gene is believed to be the human homologue of yeast GAA1P which anchors proteins to cell surface membranes by glycosylphosphatidylinositols (GPIs). See, for example, Yeast Gaa1p is required for attachment of a completed GPI anchor onto proteins (J Cell Biol. 1995 May; 129(3): 629-639. PMID: 7730400; UI: 95247814).

This gene is expressed primarily in primary breast cancer and to a lesser extent in amniotic cells.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, breast cancer. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the metabolic system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., reproductive tissue, amniotic cells and tissue and cancerous and wounded tissues) or bodily fluids (e.g., breast milk, lymph, amniotic fluid, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO:102 as residues: Pro-113 to Met-123.

The tissue distribution and similarity to GAA1P indicates that polynucleotides and polypeptides corresponding to this gene are useful for diagnosis and treatment of primary breast cancers. Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:30 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general

formula of a-b, where a is any integer between 1 to 2128 of SEQ ID NO:30, b is an integer of 15 to 2142, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:30, and where the b is greater than or equal to a + 14.

## 5 FEATURES OF PROTEIN ENCODED BY GENE NO: 21

This gene is expressed primarily in activated T-cells and to a lesser extent in prostate cancer and HSC172 cells.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a  
10 biological sample and for diagnosis of diseases and conditions which include, but are not limited to, immune dysfunction and/or prostate cancer. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune and metabolic systems,  
15 expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., cells and tissue of the immune system, reproductive tissue, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, seminal fluid, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene  
20 expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO:103 as residues: Ala-17 to Pro-26, Phe-92 to Tyr-97, Gly-104 to Glu-111.

The tissue distribution indicates that polynucleotides and polypeptides  
25 corresponding to this gene are useful for diagnosis and treatment of immune disorders and/or prostate cancer. Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:31 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically  
30 excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1550 of SEQ ID NO:31, b is an integer of 15 to 1564, where both a and b correspond to the positions of nucleotide  
35 residues shown in SEQ ID NO:31, and where the b is greater than or equal to a + 14.

**FEATURES OF PROTEIN ENCODED BY GENE NO: 22**

This gene maps to chromosome 12, and therefore, may be used as a marker in linkage analysis for chromosome 12.

5 This gene is expressed primarily in breast tissues and to a lesser extent in fetal spleen.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, breast cancer, lactation deficiencies, and other breast related diseases, including breast cancer. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the haemolymphoid and reproductive systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., breast tissue, cells and tissue of the immune system, and haemolymphoid tissue, cancerous and wounded tissues) or bodily fluids (e.g., lymph, breast milk, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level; i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in tumors of breast origins indicates that polynucleotides and polypeptides corresponding to this gene are useful for diagnosis and intervention of these tumors, in addition to other tumors where expression has been indicated. Protein, as well as, antibodies directed against the protein may show utility as a tissue-specific marker and/or immunotherapy target for the above listed tissues. Alternatively, The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for the treatment and diagnosis of hematopoietic related disorders such as anemia, pancytopenia, leukopenia, thrombocytopenia or leukemia since stromal cells are important in the production of cells of hematopoietic lineages. The uses include bone marrow cell ex vivo culture, bone marrow transplantation, bone marrow reconstitution, radiotherapy or chemotherapy of neoplasia. The gene product may also be involved in lymphopoiesis, therefore, it can be used in immune disorders such as infection, inflammation, allergy, immunodeficiency etc. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Many polynucleotide sequences, such as EST sequences, are publicly available

and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:32 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome.

- 5 Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1617 of SEQ ID NO:32, b is an integer of 15 to 1631, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:32, and where the b is greater than or equal to a + 14.

10

### FEATURES OF PROTEIN ENCODED BY GENE NO: 23

- The translation product of this gene shares sequence homology with mutant or polymorphic BRCA1 gene which is thought to be important in the diagnosis and therapy of human breast and ovarian cancer as a predisposing gene (See Genebank  
15 Accession No T17455). This gene maps to chromosome 18, and therefore, may be used as a marker in linkage analysis for chromosome 18.

This gene is expressed primarily in primary dendritic cells.

- Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a  
20 biological sample and for diagnosis of diseases and conditions which include, but are not limited to, breast, ovarian, and other reproductive related disorders and cancers. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the  
25 haemolymphoid and reproductive systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., reproductive tissue, pleural tissue, breast tissue, and cancerous and wounded tissues) or bodily fluids (e.g., breast milk, lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a  
30 disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO:105 as residues: Pro-13 to Lys-18, Ala-50 to Leu-58.

- The homology to the mutant or polymorphic BRCA1 gene indicates that  
35 polynucleotides and polypeptides corresponding to this gene are useful for diagnosis and intervention of breast and/or ovarian tumors, in addition to other tumors where



expression has been indicated. Protein, as well as, antibodies directed against the protein may show utility as a tissue-specific marker and/or immunotherapy target for the above listed tissues. Alternatively, the tissue distribution within dendritic cells indicates that the protein product of this gene is useful for the detection/treatment of

5 neurodegenerative disease states and behavioral disorders such as Alzheimers Disease, Parkinsons Disease, Huntingtons Disease, Tourette Syndrome, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition, the gene or gene product

10 may also play a role in the treatment and/or detection of developmental disorders associated with the developing embryo, sexually-linked disorders, or disorders of the cardiovascular system. Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:33 and may have been publicly available prior to conception

15 of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 964 of SEQ ID NO:33, b is an

20 integer of 15 to 978, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:33, and where the b is greater than or equal to a + 14.

#### FEATURES OF PROTEIN ENCODED BY GENE NO: 24

The translation product of this gene shares sequence homology with smaller

25 hepatocellular oncoprotein which is thought to be important in protein synthesis (See Genebank Accession No. R07057). One embodiment of this gene comprises polypeptides of the following amino acid sequence: LRSVVQDHPGQHGETPSLLKIQ @ (SEQ ID NO:161). An additional embodiment is the polynucleotides encoding these polypeptides.

30 This gene is expressed primarily in embryonic tissues and to a lesser extent in uterine cancer.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are

35 not limited to, hepatocellular tumors, and other disorders characterized by proliferating and/or developing tissues. Similarly, polypeptides and antibodies directed to these

polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the haemolymphoid system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., reproductive tissue, cells and tissue of the immune system, and cancerous and wounded tissues) or bodily fluids (e.g., amniotic fluid, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO:106 as residues: Asn-15 to Ser-20, Ile-32 to Asn-37.

The tissue distribution combine with the homology to a conserved human hepatocellular oncoprotein indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and treatment of cancer and other proliferative disorders. Expression within embryonic tissue and other cellular sources marked by proliferating cells indicates that this protein may play a role in the regulation of cellular division. Additionally, the expression also indicates that this protein may play a role in the proliferation, differentiation, and/or survival of hematopoietic cell lineages. In such an event, this gene may be useful in the treatment of lymphoproliferative disorders, and in the maintenance and differentiation of various hematopoietic lineages from early hematopoietic stem and committed progenitor cells. Similarly, embryonic development also involves decisions involving cell differentiation and/or apoptosis in pattern formation. Thus this protein may also be involved in apoptosis or tissue differentiation and could again be useful in cancer therapy. Alternatively, the homology to a hepatocellular protein indicates that the protein product of this gene is useful for the detection and treatment of liver disorders and cancers (e.g. hepatoblastoma, jaundice, hepatitis, liver metabolic diseases and conditions that are attributable to the differentiation of hepatocyte progenitor cells). In addition the expression in fetus would suggest a useful role for the protein product in developmental abnormalities, fetal deficiencies, pre-natal disorders and various wound-healing models and/or tissue trauma. Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:34 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or

more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 884 of SEQ ID NO:34, b is an integer of 15 to 898, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:34, and where the b is greater than or equal to a + 14.

5

#### FEATURES OF PROTEIN ENCODED BY GENE NO: 25

The translation product of this gene shares sequence homology with a gene encoding for anti-heparanase activity which is thought to be important in inhibition of heparin or heparan sulphate degradation. Moreover, this gene was shown to have  
10 homology to the human 3-oxo-5-beta-steroid 4-dehydrogenase, which is known to be important in metabolism since it catalyzes the reduction of delta(4) double bonds of bile acid intermediates and steroid hormones carrying the delta(4)-3-one structure in the A/B Cis configuration (See Genebank Accession No. Z28339) One embodiment of this gene comprises polypeptides of the following amino acid sequence:

15 MFYNFVRQLDTVSIHAGKSKLKMTVGTKLTSGXGPRKSSQSGRIAASITDCQ  
QCKA @ (SEQ ID NO:162), and/or  
MEAILPLWLLFLGPXPEVSFVPTVIFNLDFPACSLTVSSCLTKL @ (SEQ ID  
NO:163). An additional embodiment is the polynucleotides encoding these  
polypeptides.

20 This gene is expressed primarily in fetal tissues.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, arthritis, metabolic disorders, as well as reproductive disorders.

25 Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the haemolymphoid system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. reproductive, metabolic,  
30 cancerous and wounded tissues) or bodily fluids (e.g., bile acid, amniotic fluid, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

35 The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and treatment of cancer and other

proliferative disorders. Expression within embryonic tissue and other cellular sources marked by proliferating cells indicates that this protein may play a role in the regulation of cellular division. Additionally, the expression indicates that this protein may play a role in the proliferation, differentiation, and/or survival of hematopoietic cell lineages.

5 In such an event, this gene may be useful in the treatment of lymphoproliferative disorders, and in the maintenance and differentiation of various hematopoietic lineages from early hematopoietic stem and committed progenitor cells. Similarly, embryonic development also involves decisions involving cell differentiation and/or apoptosis in pattern formation. Thus this protein may also be involved in apoptosis or tissue  
10 differentiation and could again be useful in cancer therapy. Alternatively, based upon its homology to a conserved human anti-heparanase gene, mutations of which are known to be important in the predisposition of arthritis, may suggest that this protein may also be important in the diagnosis or treatment of various autoimmune disorders such as rheumatoid arthritis, lupus, scleroderma, and dermatomyositis as well as dwarfism,  
15 spinal deformation, and specific joint abnormalities as well as chondrodysplasias i.e. spondyloepiphyseal dysplasia congenita, familial osteoarthritis, Atelosteogenesis type II, metaphyseal chondrodysplasia type Schmid. Moreover, the homology to a conserved human metabolic gene may suggest that the protein product of this gene is useful for the diagnosis, prevention, and/or treatment of various metabolic disorders  
20 such as Tay-Sachs disease, phenylketonuria, galactosemia, porphyrias, and Hurler's syndrome. Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:35 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded  
25 from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 740 of SEQ ID NO:35, b is an integer of 15 to 754, where both a and b correspond to the positions of nucleotide residues shown in  
30 SEQ ID NO:35, and where the b is greater than or equal to a + 14.

#### FEATURES OF PROTEIN ENCODED BY GENE NO: 26

The translation product of this gene shares sequence homology with pulmonary hydrophobic surfactant-associated proteins which is thought to be important in useful  
35 for normalising pulmonary surface tension (See Genebank Accession No. N80643 ).

This gene is expressed primarily in embryonic tissues.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, hyaline membrane disease, developmental and pulmonary disorders.

5 Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the respiratory system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., pulmonary tissue, developing  
10 tissue and cancerous and wounded tissues) or bodily fluids (e.g., surfactant, amniotic fluid, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

15 The tissue distribution and homology to pulmonary hydrophobic surfactant-associated proteins indicates that polynucleotides and polypeptides corresponding to this gene are useful for the treatment and diagnosis of such lung related diseases such as hyaline membrane disease which is often characteristic of premature infants - leading to significant pulmonary disorders throughout childhood. Alternatively, The tissue  
20 distribution indicates that polynucleotides and polypeptides corresponding to this gene are . useful for the diagnosis and treatment of cancer and other proliferative disorders. Expression within embryonic tissue and other cellular sources marked by proliferating cells indicates that this protein may play a role in the regulation of cellular division. Additionally, the expression indicates that this protein may play a role in the  
25 proliferation, differentiation, and/or survival of hematopoietic cell lineages. In such an event, this gene may be useful in the treatment of lymphoproliferative disorders, and in the maintenance and differentiation of various hematopoietic lineages from early hematopoietic stem and committed progenitor cells. Similarly, embryonic development also involves decisions involving cell differentiation and/or apoptosis in pattern  
30 formation. Thus this protein may also be involved in apoptosis or tissue differentiation and could again be useful in cancer therapy. Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:36 and may have been publicly available prior to conception of the present invention. Preferably, such related  
35 polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the

present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 685 of SEQ ID NO:36, b is an integer of 15 to 699, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:36, and where the b is greater than or equal to a + 14.

#### FEATURES OF PROTEIN ENCODED BY GENE NO: 27

This gene is expressed primarily in fetal tissue and to a lesser extent in thymus.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, immunological disorders, particularly immunodeficiency. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the haemolymphoid system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., cells and tissue of the immune system, developing tissue, and cancerous and wounded tissues) or bodily fluids (e.g., amniotic fluid, lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO:109 as residues: Pro-18 to Trp-24.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and treatment of a variety of immune system disorders. Expression of this gene product in thymus indicates a role in the regulation of the proliferation; survival; differentiation; and/or activation of potentially all hematopoietic cell lineages, including blood stem cells. This gene product may be involved in the regulation of cytokine production, antigen presentation, or other processes that may also suggest a usefulness in the treatment of cancer (e.g. by boosting immune responses). Since the gene is expressed in cells of lymphoid origin, the natural gene product may be involved in immune functions. Therefore it may be also used as an agent for immunological disorders including arthritis, asthma, immune deficiency diseases such as AIDS, and leukemia. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tumors and tissues. In addition, this gene product may have

commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:37 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 957 of SEQ ID NO:37, b is an integer of 15 to 971, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:37, and where the b is greater than or equal to a + 14.

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 28**

This gene is expressed primarily in small intestine and to a lesser extent in ulcerative colitis.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, ulcers, acid reflux and other gastrointestinal disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the digestive system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., gastrointestinal tissue, and cancerous and wounded tissues) or bodily fluids (e.g., bile, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO:110 as residues: Ile-2 to Ser-8, Gln-23 to Ser-31, Lys-61 to Lys-66, Lys-74 to Thr-79, Val-138 to Glu-160, Glu-178 to Thr-183.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for the treatment and diagnosis of digestive and

gastrointestinal problems such as acid reflux or ulcers. Alternatively, the tissue distribution may suggest that the protein product of this gene is useful for the diagnosis, prevention, and/or treatment of various metabolic disorders such as Tay-Sachs disease, phenylketonuria, galactosemia, porphyrias, and Hurler's syndrome.

- 5 Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:38 and may have been publicly available prior to conception of the present invention. Preferably, 10 such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 858 of SEQ ID NO:38, b is an integer of 15 to 872, where both a and b 15 correspond to the positions of nucleotide residues shown in SEQ ID NO:38, and where the b is greater than or equal to a + 14.

#### FEATURES OF PROTEIN ENCODED BY GENE NO: 29

- The translation product of this gene was shown to have homology to catalase 20 (See Genbank Accession No. pirlA55092|A55092) which is known to play an integral role in the oxidative prophylaxis in eukaryotic and mammalian cells. One embodiment of this gene comprises polypeptides of the following amino acid sequence:  
NHGHSCFLCEIVIRSQFHTTYEPEA @ (SEQ ID NO:164), and/or  
SGRHRVELQLLFPLVRVNFELGVNHGHSCFLCEIVIRSQFHTTYEPEA @ (SEQ 25 ID NO:165). An additional embodiment is the polynucleotides encoding these polypeptides. This gene maps to chromosome 3, and therefore, may be used as a marker in linkage analysis for chromosome 3.

This gene is expressed primarily in skin and to a lesser extent in human uterine cancer.

- 30 Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, uterine cancer; fibrosis; melanoma. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes 35 for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the epidermis and/or reproductive system,



expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., integumentary tissue, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution combined with the homology to catalase indicates that polynucleotides and polypeptides corresponding to this gene are useful for the treatment and/or diagnosis of human uterine cancer and potentially, all cancers in general (particularly of the epidermis) due to the fact that diminished catalase activity has been shown to lead to significant cellular damage which could predispose cancer. Likewise, this gene and/or its protein product may be useful in the treatment and/or diagnosis of other disorders of the skin, such as fibrosis or in wound healing. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:39 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 594 of SEQ ID NO:39, b is an integer of 15 to 608, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:39, and where the b is greater than or equal to a + 14.

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 30**

This gene is expressed primarily in fetal liver/spleen and bone marrow stromal cells, and to a lesser extent in neural tissues (brain; spinal cord) and cancers (glioblastoma; chondrosarcoma).

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, cancers, particularly of glial cells and cartilage; hematopoietic and other immune disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the

tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the hematopoietic/immune system and CNS, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., hematopoietic cells and tissue, and cancerous and wounded tissues) or  
5 bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO:112 as residues: Arg-2 to Asp-7.

10 The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for the expansion, proliferation, and/or differentiation of hematopoietic cells. This gene is expressed predominantly at sites of hematopoiesis, such as fetal liver and bone marrow, and thus may control the proliferation and/or differentiation of hematopoietic stem and progenitor cells. Thus it  
15 could be used for chemoprotection, or for the production of specific blood cell lineages, as well as the amplification of stem cells. Additionally, its expression in neural cells of the brain and spinal cord suggest that it may also play a role in the maintenance and differentiation of neuronal stem cells, or in the treatment of neurological disorders, such as Alzheimers Disease, Parkinsons Disease, Huntingtons Disease, Tourette Syndrome,  
20 schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition, the gene or gene product may also play a role in the treatment and/or detection of developmental disorders associated with the developing embryo, sexually-linked  
25 disorders, or disorders of the cardiovascular system. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. Finally, its observed expression in various cancers suggest that it may play a role in the control of cell proliferation. Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through  
30 sequence databases. Some of these sequences are related to SEQ ID NO:40 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a  
35 nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 841 of SEQ ID NO:40, b is an integer of 15 to 855, where both a and b

correspond to the positions of nucleotide residues shown in SEQ ID NO:40, and where the b is greater than or equal to a + 14.

### FEATURES OF PROTEIN ENCODED BY GENE NO: 31

5        This gene is expressed primarily in placenta, bone marrow, and fetal liver/spleen and to a lesser extent in brain and CNS.

         Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, hematopoietic disorders; placental insufficiency; neurological disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system and/or CNS, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., hematopoietic cells and tissue, cells and tissue of the immune system, and neurological tissue, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, amniotic fluid, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO:113 as residues: Arg-53 to Gln-58.

         The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for the proliferation, maintenance, and/or differentiation of hematopoietic cells. In addition, it may be involved in the maintenance and establishment of the vasculature, and may play a role in the regulation of angiogenesis. Thus, it may play a role in the establishment and/or maintenance of tumors. Expression in the CNS indicates that this gene product may also be useful in the treatment of neurodegenerative disorders, such as Alzheimers Disease, Parkinsons Disease, Huntingtons Disease, Tourette Syndrome, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition, the gene or gene product may also play a role in the treatment and/or detection of developmental disorders associated with the developing embryo, sexually-linked disorders, or disorders of the cardiovascular system. Protein, as well as, antibodies directed against the protein may show utility as a

tumor marker and/or immunotherapy targets for the above listed tissues. Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:41 and may have been publicly available prior to conception of the present invention.

- 5 Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1028 of SEQ ID NO:41, b is an integer of 15 to 1042, where  
10 both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:41; and where the b is greater than or equal to a + 14.

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 32**

- 15 The translation product of this gene was shown to have homology to the ras-related protein RABB from Dictyostelium discoideum (See Genebank Accession No.P34142). Members of the Ras family of proteins are known to be essential to normal cell cycle control and mutations of which have been shown to lead to the predisposition of cancer.

This gene is expressed primarily in Jurkat T cells.

- 20 Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, T cell lymphomas; defects in immune surveillance and/or T cell activation. Similarly, polypeptides and antibodies directed to these polypeptides  
25 are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., cells and tissue of the immune system, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum,  
30 plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

- 35 The tissue distribution combined with its homology to a Ras-related protein indicates that polynucleotides and polypeptides corresponding to this gene are useful for the treatment of defects in immune surveillance and cancer. Expression of this gene

product in T cells indicates that it represents a secreted protein that may regulate T cells in an autocrine fashion, thereby impacting on their ability to recognize antigen and become activated, or may be involved in immune modulation. Likewise, this may represent a secreted protein made by T cells that affects other hematopoietic cells and regulates their proliferation and/or differentiation. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:42 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 688 of SEQ ID NO:42, b is an integer of 15 to 702, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:42, and where the b is greater than or equal to a + 14.

#### FEATURES OF PROTEIN ENCODED BY GENE NO: 33

The translation product of this gene shares sequence homology with a known human spliceosome associated protein (See Genebank Accession No. AA523942) as well as a yeast protein (ORF YBR173c [*Saccharomyces cerevisiae*]). Preferred polypeptides comprise the following amino acid sequence:  
MNARGLGSELKDSIPVTELSASGPFES  
HDLLRKGFCVKNELLP SHPLELSEKNFQLNQDKMNFSTLRNIQGLFAPLKLQ  
MEFKAVQQVQRLPFLSSSNLSLDVLRGNDETIGFEDILNDPSQSEVMGEPHLMV  
EYKLGLL (SEQ ID NO:166). Also preferred are the polynucleotides encoding these polypeptides.

This gene is expressed primarily in bone marrow and stromal cells, and to a lesser extent in T cells and peripheral blood cells.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, hematopoietic disorders; leukemias; defects in immune surveillance; defects in T cell activation; inflammation; bacterial infections, and other disorders characterized by immunodeficiency. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential

identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., cells and tissue of the immune system, and cancerous and wounded  
5 tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO:115 as residues: Lys-16 to Thr-24.

10 The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for the proliferation, differentiation, and/or activation of hematopoietic cell lineages. Such treatments could involve chemoprotection or expansion of either progenitor cells or specific mature blood lineages. Likewise, this gene product could be involved in immune modulation, or in  
15 affecting T cell activation and antigen recognition. Alternatively, the protein product of this gene is useful for the treatment and diagnosis of hematopoietic related disorders such as anemia, pancytopenia, leukopenia, thrombocytopenia or leukemia since stromal cells are important in the production of cells of hematopoietic lineages. The uses include bone marrow cell ex vivo culture, bone marrow transplantation, bone marrow  
20 reconstitution, radiotherapy or chemotherapy of neoplasia. The gene product may also be involved in lymphopoiesis, therefore, it can be used in immune disorders such as infection, inflammation, allergy, immunodeficiency etc. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell  
25 types. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above tissues. Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:43 and may have been publicly available prior to conception of the present invention. Preferably,  
30 such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 628 of SEQ ID NO:43, b is an integer of 15 to 642, where both a and b  
35 correspond to the positions of nucleotide residues shown in SEQ ID NO:43, and where the b is greater than or equal to a + 14.

**FEATURES OF PROTEIN ENCODED BY GENE NO: 34**

This gene maps to chromosome 4, and therefore, may be used as a marker in linkage analysis for chromosome 4.

5 This gene is expressed primarily in placenta and brain, and to a lesser extent in specific tumors and cancers (kidney, colorectal, colon, osteoclastoma).

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, tumors of the kidney, colon, and bone; neurological disorders; defects of the vasculature. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the vasculature and CNS, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., reproductive tissue, cells and tissue of the immune system, neural tissue, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, amniotic fluid, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for the treatment of neurological disorders, such as Alzheimers or schizophrenia. Expression of this gene in the placenta may indicate a role in fetal development, or may simply be a hallmark of expression in the vasculature. Expression of this gene product in endothelial cells may indicate secretion of the protein product into the circulation, where it may have effects on circulating blood cells, or on tissues at distant locations. At such sites, it may control cellular proliferation and/or differentiation. In addition, expression in a variety of tumors indicates that this gene product may play a role in cellular proliferation. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:44 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related

sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1205 of SEQ ID NO:44, b is an integer of 15 to 1219, where both a and b correspond to the positions of  
5 nucleotide residues shown in SEQ ID NO:44, and where the b is greater than or equal to a + 14.

### FEATURES OF PROTEIN ENCODED BY GENE NO: 35

This gene is expressed primarily in macrophages, treated with GM-CSF.

10 Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, immune deficiencies; susceptibility to bacterial infections; improper stimulation of lymphocyte pools. Similarly, polypeptides and antibodies directed to  
15 these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., cells and tissue of the immune system, and cancerous and wounded  
20 tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO:117 as residues: Arg-48 to Asn-56.

25 The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for the regulation and/or stimulation of hematopoietic cells, particularly the circulating lymphocytes. Macrophages are one of the front lines of immune defense, particularly against bacterial pathogens, and are able to secrete cytokines and proteins that affect other blood cells. Thus, this gene product  
30 may be important in regulation of the immune system, in activation of hematopoietic cells, such as T cells; and may play a role in antigen recognition. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence  
35 databases. Some of these sequences are related to SEQ ID NO:45 and may have been publicly available prior to conception of the present invention. Preferably, such related



polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 423 of  
5 SEQ ID NO:45, b is an integer of 15 to 437, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:45, and where the b is greater than or equal to a + 14.

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 36**

10 This gene is expressed primarily in endothelial cells.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, inflammation and circulatory system disorders. Similarly, polypeptides  
15 and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the circulatory system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., endothelial cells, cancerous and wounded tissues) or bodily  
20 fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution indicates that polynucleotides and polypeptides  
25 corresponding to this gene are useful for diagnosis and treatment of inflammatory disorders involving endothelial cells, such as sepsis, inflammatory bowel diseases, psoriasis, and rheumatoid arthritis as well as atherosclerosis, which can lead to strokes and heart attacks. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues  
30 Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:46 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome.  
35 Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of

a-b, where a is any integer between 1 to 519 of SEQ ID NO:46, b is an integer of 15 to 533; where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:46, and where the b is greater than or equal to a + 14.

## 5 FEATURES OF PROTEIN ENCODED BY GENE NO: 37

The translation product of this gene was shown to have homology to the human transducin(beta)-like 1. protein (See Genebank Accession No P38262).

This gene is expressed primarily in fetal lung and to a lesser extent in adult lung and breast.

10 Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, respiratory system diseases, and/or disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological  
15 probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the respiratory system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., pulmonary tissue, and cancerous and wounded tissues) or bodily fluids (e.g., pulmonary surfactant, serum, plasma, urine, synovial fluid and  
20 spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for diagnosis and disease affecting the lung such  
25 as lung cancer, emphysema, pulmonary edema, asthma, cystic fibrosis, and pulmonary emboli. Alternatively, the protein product of this gene may be useful in the detection, treatment, and/or prevention of various inflammatory conditions afflicting endothelial tissue such as the vasculature and cardiovascular systems. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or  
30 immunotherapy targets for the above listed tissues. Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:47 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To  
35 list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence

described by the general formula of a-b, where a is any integer between 1 to 1835 of SEQ ID NO:47, b is an integer of 15 to 1849, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:47, and where the b is greater than or equal to a + 14.

5

### FEATURES OF PROTEIN ENCODED BY GENE NO: 38

This gene is expressed primarily in prostate cancer and to a lesser extent in osteoblasts.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, prostate cancer, osteoporosis. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the reproductive system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., skeletal tissue, reproductive tissue, and cancerous and wounded tissues) or bodily fluids (e.g., seminal fluid, lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in tumors of prostate origins indicates that polynucleotides and polypeptides corresponding to this gene are useful for diagnosis and intervention of these tumors, in addition to other tissues where expression has been indicated. Protein, as well as, antibodies directed against the protein may show utility as a tissue-specific marker and/or immunotherapy target for the above listed tissues. Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:48 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 912 of SEQ ID NO:48, b is an integer of 15 to 926, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:48, and where the b is greater than or equal to a + 14.

**FEATURES OF PROTEIN ENCODED BY GENE NO: 39**

The translation product of this gene was shown to have homology to the mdck-1 protein from *Mus musculus* (See Genbank Accession No. gil2736292 (AF030433)) which has been shown to be important as a possible homeobox gene inducer specific to head development. One embodiment of this gene comprises polypeptides of the following amino acid sequence: GGNKYQTIDNYQPYP @ (SEQ ID NO:167), PLLGVSATLNSVLNSNAIKN @ (SEQ ID NO:168), and/or GSAVSAAPGILYPG. An additional embodiment is the polynucleotides encoding these polypeptides (SEQ ID NO:169).

This gene is expressed primarily in placenta and to a lesser extent in smooth muscle.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, developmental disorders of the fetus, and/or reproductive disorders, particularly of the female. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of developing tissues in the fetus, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., reproductive tissue, and cancerous and wounded tissues) or bodily fluids (e.g., amniotic fluid, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution combined with the homology to a suspected homeobox domain inducer indicates that polynucleotides and polypeptides corresponding to this gene are useful for diagnosis and treatment of developmental disorders, particularly those involving hematopoiesis and pattern formation in the embryo. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:49 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To

list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1579 of SEQ ID NO:49, b is an integer of 15 to 1593, where both a and b correspond to the  
5 positions of nucleotide residues shown in SEQ ID NO:49, and where the b is greater than or equal to a + 14.

### FEATURES OF PROTEIN ENCODED BY GENE NO: 40

When tested against sensory neuron cell lines (PC12), supernatants removed  
10 from cells containing this gene activated the early growth response gene 1 pathway (EGR1). Thus, it is likely that this gene activates neuronal cells through the Jaks-STAT signal transduction pathway. EGR1 (early growth response gene 1) is a separate signal transduction pathway from Jaks-STAT, genes containing the EGR1 promoter are induced in various tissues and cell types upon activation, leading the cells to undergo  
15 differentiation and proliferation.

This gene is expressed primarily in neutrophils and to a lesser extent in pancreatic carcinoma.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a  
20 biological sample and for diagnosis of diseases and conditions which include, but are not limited to, inflammation, gastrointestinal, and immune disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system,  
25 expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., cells and tissue of the immune system, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e.,  
30 the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO:122 as residues: Pro-8 to Ala-16.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and treatment of a variety of  
35 immune system disorders. Expression of this gene product in tonsils indicates a role in the regulation of the proliferation; survival; differentiation; and/or activation of

potentially all hematopoietic cell lineages, including blood stem cells. This gene product may be involved in the regulation of cytokine production, antigen presentation, or other processes that may also suggest a usefulness in the treatment of cancer (e.g. by boosting immune responses). Since the gene is expressed in cells of lymphoid origin, the natural gene product may be involved in immune functions. Therefore it may be also used as an agent for immunological disorders including arthritis, asthma, immune deficiency diseases such as AIDS, and leukemia. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tumors and tissues. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:50 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 964 of SEQ ID NO:50, b is an integer of 15 to 978, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:50, and where the b is greater than or equal to a + 14.

## **25 FEATURES OF PROTEIN ENCODED BY GENE NO: 41**

This gene is expressed primarily in breast lymph node and to a lesser extent in anergic T-cell.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, inflammation, and immunodeficiency disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., cells and tissue of the immune system, and cancerous and

wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

5       The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and treatment of a variety of immune system disorders. Expression of this gene product in T-cells indicates a role in the regulation of the proliferation; survival; differentiation; and/or activation of potentially all hematopoietic cell lineages, including blood stem cells. This gene product  
10       may be involved in the regulation of cytokine production, antigen presentation, or other processes that may also suggest a usefulness in the treatment of cancer (e.g. by boosting immune responses). Since the gene is expressed in cells of lymphoid origin, the natural gene product may be involved in immune functions. Therefore it may be also used as an agent for immunological disorders including arthritis, asthma, immune  
15       deficiency diseases such as AIDS, leukemia, rheumatoid arthritis, inflammatory bowel disease, sepsis, acne, and psoriasis. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tumors and tissues. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in  
20       the differentiation and/or proliferation of various cell types. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:51 and may have been  
25       publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 419 of  
30       SEQ ID NO:51, b is an integer of 15 to 433, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:51, and where the b is greater than or equal to a + 14.

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 42**

35       This gene is expressed primarily in synovium.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, inflammation and diseases of the joints. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system and connective tissue, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., skeletal tissue, and cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for diagnosis and treatment of inflammatory disorders, particularly those involving the joints and skeletal system, such as rheumatoid arthritis and in particular the connective tissues (e.g. trauma, tendonitis, chondromalacia). Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. . Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:52 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 847 of SEQ ID NO:52, b is an integer of 15 to 861, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:52, and where the b is greater than or equal to a + 14.

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 43**

This gene maps to chromosome 5, and therefore, may be used as a marker in linkage analysis for chromosome 5.

This gene is expressed primarily in synovium.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a



biological sample and for diagnosis of diseases and conditions which include, but are not limited to, diseases of the joints and connective tissues. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., skeletal tissue, and cancerous and wounded tissues) or bodily fluids (e.g. serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for diagnosis and treatment of inflammatory joint disorders as well as suggest a role in the detection and treatment of disorders and conditions affecting the skeletal system, in particular the connective tissues (e.g. arthritis, trauma, tendonitis, chondromalacia and inflammation). Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:53 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 496 of SEQ ID NO:53, b is an integer of 15 to 510, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:53, and where the b is greater than or equal to a + 14.

#### **30 FEATURES OF PROTEIN ENCODED BY GENE NO: 44**

This gene is expressed primarily in activated T cells.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, inflammation and other immune system disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing

immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., cells and tissue of the immune system, and  
5 cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID  
10 NO:126 as residues: Met-1 to Lys-7.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and treatment of a variety of immune system disorders. Expression of this gene product in T-cells indicates a role in the regulation of the proliferation; survival; differentiation; and/or activation of  
15 potentially all hematopoietic cell lineages, including blood stem cells. This gene product may be involved in the regulation of cytokine production, antigen presentation, or other processes that may also suggest a usefulness in the treatment of cancer (e.g. by boosting immune responses). Since the gene is expressed in cells of lymphoid origin, the natural gene product may be involved in immune functions. Therefore it may be also  
20 used as an agent for immunological disorders including arthritis, asthma, immune deficiency diseases such as AIDS, leukemia, rheumatoid arthritis, inflammatory bowel disease, sepsis, acne, and psoriasis. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tumors and tissues. In addition, this gene product may have commercial utility in  
25 the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence  
30 databases. Some of these sequences are related to SEQ ID NO:54 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence  
35 described by the general formula of a-b, where a is any integer between 1 to 295 of SEQ ID NO:54, b is an integer of 15 to 309, where both a and b correspond to the

positions of nucleotide residues shown in SEQ ID NO:54, and where the b is greater than or equal to a + 14.

#### FEATURES OF PROTEIN ENCODED BY GENE NO: 45

5           This gene is expressed primarily in placenta, liver, lung, endometrial stromal cell and embryo.

          Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions such as cancers,  
10   immunodeficiency and autoimmune diseases, as well as reproductive and hepatic disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may  
15   be routinely detected in certain tissues or cell types (e.g., reproductive tissue, and cancerous and wounded tissues) or bodily fluids (e.g., amniotic fluid, bile, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not  
20   having the disorder.

          The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for the detection and treatment of liver disorders and cancers (e.g. hepatoblastoma, jaundice, hepatitis, liver metabolic diseases and conditions that are attributable to the differentiation of hepatocyte progenitor cells). In  
25   addition the expression in fetus would suggest a useful role for the protein product in developmental abnormalities, fetal deficiencies, pre-natal disorders and various wound-healing models and/or tissue trauma. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. Many polynucleotide sequences, such as EST sequences, are publicly  
30   available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:55 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more  
35   polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1571 of SEQ ID NO:55, b is an integer of 15

to 1585, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:55, and where the b is greater than or equal to a + 14.

#### FEATURES OF PROTEIN ENCODED BY GENE NO: 46

5 This gene is expressed primarily in placenta, amniotic cells and adrenal gland tumor.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions such as cancers, as well  
10 as various reproductive and endocrine disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell  
15 types (e.g., endocrine tissue, reproductive tissue, and cancerous and wounded tissues) or bodily fluids (e.g., amniotic fluid, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include  
20 those comprising a sequence shown in SEQ ID NO:128 as residues: Cys-52 to Val-61.

The tissue distribution within placenta and amniotic tissues indicates that polynucleotides and polypeptides corresponding to this gene useful for the treatment and diagnosis of reproductive disorders, particularly those of the female reproductive system, including cancer and tissues characteristic of the developing embryo. In  
25 addition, the tissue distribution within the adrenal gland indicates that the protein product of this gene is useful for the detection, treatment, and/or prevention of various endocrine disorders and cancers, particularly Addison's disease, Cushing's Syndrome, and disorders and/or cancers of the pancreas (e.g. diabetes mellitus), adrenal cortex, ovaries, pituitary (e.g., hyper-, hypopituitarism), thyroid (e.g. hyper-,  
30 hypothyroidism), parathyroid (e.g. hyper-,hypoparathyroidism) , hypothalamus, and testes. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:56 and  
35 may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the

present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 860 of SEQ ID NO:56, b is an integer of 15 to 874, where  
5 both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:56, and where the b is greater than or equal to a + 14.

#### FEATURES OF PROTEIN ENCODED BY GENE NO: 47

This gene is expressed primarily in melanocyte, melanoma, dendritic cells and  
10 fetal brain.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, skin disorders, particularly melanoma, as well as neurodegenerative  
15 disorders and cancer. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell  
20 types (e.g., neural tissue, integumentary tissue, and cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those  
25 comprising a sequence shown in SEQ ID NO:129 as residues: Lys-76 to Gly-81.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for the treatment, diagnosis, and/or prevention of various skin disorders including congenital disorders (i.e. nevi, moles, freckles, Mongolian spots, hemangiomas, port-wine syndrome), integumentary tumors (i.e.  
30 keratoses, Bowen's disease, basal cell carcinoma, squamous cell carcinoma, malignant melanoma, Paget's disease, mycosis fungoides, and Kaposi's sarcoma), injuries and inflammation of the skin (i.e., wounds, rashes, prickly heat disorder, psoriasis, dermatitis), atherosclerosis, urticaria, eczema, photosensitivity, autoimmune disorders (i.e. lupus erythematosus, vitiligo, dermatomyositis, morphea, scleroderma,  
35 pemphigoid, and pemphigus), keloids, striae, erythema, petechiae, purpura, and xanthelasma. Moreover, such disorders may predispose increased susceptibility to viral

and bacterial infections of the skin (i.e. cold sores, warts, chickenpox, molluscum contagiosum, herpes zoster, boils, cellulitis, erysipelas, impetigo, tinea, athletes foot, and ringworm). Alternatively, the tissue distribution within dendritic cells and fetal brain indicates that the protein product of this gene is useful for the detection/treatment of neurodegenerative disease states and behavioral disorders such as Alzheimers Disease, Parkinsons Disease, Huntingtons Disease, Tourette Syndrome, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition, the gene or gene product may also play a role in the treatment and/or detection of developmental disorders associated with the developing embryo, sexually-linked disorders, or disorders of the cardiovascular system. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:57 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1155 of SEQ ID NO:57, b is an integer of 15 to 1169, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:57, and where the b is greater than or equal to a + 14.

## 25 FEATURES OF PROTEIN ENCODED BY GENE NO: 48

This gene maps to chromosome 1, and therefore, may be used as a marker in linkage analysis for chromosome 1.

This gene is expressed primarily in ovary tumors and to a lesser extent in breast, placenta, pineal gland, infant brain, T cell and B cell lymphoma.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, ovary cancer, reproductive disorders, particularly of the female reproductive system, as well as disorders of the immune system, including lymphoma and immunodeficiencies. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential

identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system and female reproductive system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., reproductive, endocrine tissue, cells and tissue of  
5 the immune system, and cancerous and wounded tissues) or bodily fluids (e.g., amniotic fluid, lymph, breast milk, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include  
10 those comprising a sequence shown in SEQ ID NO:130 as residues: Asn-33 to Lys-38.

The tissue distribution in tumors of the ovary and lymph nodes, as well as, in breast and placental tissues indicates that polynucleotides and polypeptides corresponding to this gene are useful for diagnosis and intervention of such tumors, in addition to other tumors where expression has been indicated. Protein, as well as,  
15 antibodies directed against the protein may show utility as a tissue-specific marker and/or immunotherapy target for the above listed tissues. Alternatively, The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and treatment of a variety of immune system disorders. Expression of this gene product in T-cells indicates a role in the regulation of the  
20 proliferation; survival; differentiation; and/or activation of potentially all hematopoietic cell lineages, including blood stem cells. This gene product may be involved in the regulation of cytokine production, antigen presentation, or other processes that may also suggest a usefulness in the treatment of cancer (e.g. by boosting immune responses). Since the gene is expressed in cells of lymphoid origin, the natural gene  
25 product may be involved in immune functions. Therefore it may be also used as an agent for immunological disorders including arthritis, asthma, immune deficiency diseases such as AIDS, leukemia, rheumatoid arthritis, inflammatory bowel disease, sepsis, acne, and psoriasis. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed  
30 tumors and tissues. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:58 and may  
35 have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present

invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1052 of SEQ ID NO:58, b is an integer of 15 to 1066, where both a and b  
5 correspond to the positions of nucleotide residues shown in SEQ ID NO:58, and where the b is greater than or equal to a + 14.

#### FEATURES OF PROTEIN ENCODED BY GENE NO: 49

This gene is expressed primarily in breast tissue.

10 Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, breast cancer. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential  
15 identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., breast tissue and cancerous and wounded tissues) or bodily fluids (e.g., breast milk, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or  
20 cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO:131 as residues: Ala-40 to Trp-45.

The tissue distribution in breast tissue indicates that polynucleotides and  
25 polypeptides corresponding to this gene are useful for diagnosis and intervention of tumors within this tissue. Alternatively, the expression in breast may suggest that the protein product of this gene is useful for the diagnosis, treatment, and/or prevention of various reproductive system disorders, particularly of the female reproductive system. Protein, as well as, antibodies directed against the protein may show utility as a tissue-specific marker and/or immunotherapy target for the above listed tissues. Many  
30 polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:59 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the  
35 present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides



comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 758 of SEQ ID NO:59, b is an integer of 15 to 772, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:59, and where the b is greater than or equal to a + 14.

5

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 50**

This gene is expressed primarily in fetal liver, retina and to a lesser extent in thyroid and pineal gland.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, hepatic and endocrine disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the hematopoiesis and immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., liver, endocrine tissue, and cancerous and wounded tissues) or bodily fluids (e.g., bile, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO:132 as residues: Lys-9 to Trp-14.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for the detection and treatment of liver disorders and cancers (e.g. hepatoblastoma, jaundice, hepatitis, liver metabolic diseases and conditions that are attributable to the differentiation of hepatocyte progenitor cells). In addition the expression in fetus would suggest a useful role for the protein product in developmental abnormalities, fetal deficiencies, pre-natal disorders and various wound-healing models and/or tissue trauma. Alternatively, expression in pineal and thyroid glands indicates that the protein product of this gene is useful for the detection, treatment, and/or prevention of various endocrine disorders and cancers, particularly Addison's disease, Cushing's Syndrome, and disorders and/or cancers of the pancreas (e.g. diabetes mellitus), adrenal cortex, ovaries, pituitary (e.g., hyper-, hypopituitarism), thyroid (e.g. hyper-, hypothyroidism), parathyroid (e.g. hyper-, hypoparathyroidism), hypothalamus, and testes. Protein, as well as, antibodies

directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:60 and may have been publicly available  
5 prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1184 of SEQ ID NO:60, b  
10 is an integer of 15 to 1198, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:60, and where the b is greater than or equal to a + 14.

#### FEATURES OF PROTEIN ENCODED BY GENE NO: 51

15 The translation product of this gene shares sequence homology with seizure-related gene product 6 type 2 precursor which is a novel, brain-specific, gene thought to be important in the predisposition of seizures (See Genbank Accession No.gnllPIDld1006729). One embodiment of this gene comprises polypeptides of the following amino acid sequence: AGIQHELACDNPGLPENG YQILYKRLYLPGESLT  
20 FMCYEGFELMGEVTIRCILGQPSHWNGPLPVCKVAE AAAETSLEGGN @ (SEQ ID NO:170) QPSHWNGPLPVCKVAEAAAETSLEGGN @ (SEQ ID NO:171), and/or YETGETREYEVS I (SEQ ID NO:172). An additional embodiment is the polynucleotides encoding these polypeptides.

This gene is expressed primarily in brain.

25 Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, seizures and other neural and CNS disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological  
30 probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the brain, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., neural tissue, and cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample  
35 taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an

individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO:133 as residues: Cys-26 to Leu-32, Thr-49 to Ile-55, Glu-57 to Glu-63.

5 The tissue distribution in brain combined with its homology to a putative seizure gene indicates that polynucleotides and polypeptides corresponding to this gene are useful for the detection/treatment of seizures and epilepsy, including neurodegenerative disease states and behavioral disorders such as Alzheimers Disease, Parkinsons Disease, Huntingtons Disease, Tourette Syndrome, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, panic disorder, learning disabilities, ALS, 10 psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition, the gene or gene product may also play a role in the treatment and/or detection of developmental disorders associated with the developing embryo, sexually-linked disorders, or disorders of the cardiovascular system. Protein, as well as, antibodies directed against the protein may show utility as a 15 tumor marker and/or immunotherapy targets for the above listed tissues. Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:61 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the 20 present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 544 of SEQ ID NO:61, b is an integer of 15 to 558, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID 25 NO:61, and where the b is greater than or equal to a + 14.

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 52**

When tested against PC12 cell lines, supernatants removed from cells containing this gene activated the EGR1 (early growth response 1) pathway. Thus, it is 30 likely that this gene activates sensory neuron cells through the EGR1 signal transduction pathway. EGR1 is a separate signal transduction pathway from Jaks-STAT, genes containing the EGR1 promoter are induced in various tissues and cell types upon activation, leading the cells to undergo differentiation and proliferation.

This gene is expressed primarily in fetal brain.

35 Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a

biological sample and for diagnosis of diseases and conditions which include, but are not limited to, neurological disorders, particularly of the developing embryo. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the fetal brain and CNS, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO:134 as residues: Arg-16 to Thr-35.

The tissue distribution in fetal brain combined with the detected biological activity within sensory neurons indicates that polynucleotides and polypeptides corresponding to this gene are useful for the detection/treatment of neurodegenerative disease states and behavioral disorders such as Alzheimers Disease, Parkinsons Disease, Huntingtons Disease, Tourette Syndrome, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition, the gene or gene product may also play a role in the treatment and/or detection of developmental disorders associated with the developing embryo, sexually-linked disorders, or disorders of the cardiovascular system. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:62 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 602 of SEQ ID NO:62, b is an integer of 15 to 616, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:62, and where the b is greater than or equal to a + 14.

### 35 FEATURES OF PROTEIN ENCODED BY GENE NO: 53

This gene is expressed primarily in frontal cortex, and schizophrenoid brain tissue.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, Schizophrenia, and other neurodegenerative disorders, including cancer. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the brain, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., neural tissue, and cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO:135 as residues: Asp-65 to Asn-72.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for the detection/treatment of neurodegenerative disease states and behavioral disorders such as Alzheimers Disease, Parkinsons Disease, Huntingtons Disease, Tourette Syndrome, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition, the gene or gene product may also play a role in the treatment and/or detection of developmental disorders associated with the developing embryo, sexually-linked disorders, or disorders of the cardiovascular system. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:63 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 797 of SEQ ID NO:63, b is an integer of 15 to 811, where

both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:63, and where the b is greater than or equal to a + 14.

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 54**

5           This gene is expressed primarily in osteoclastoma, gall bladder, and infant brain.

          Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, Osteoclastoma, and gastrointestinal, skeletal, and neural disorders, particularly cancer. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the bone, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., skeletal tissue, neural tissue, and cancerous and wounded tissues) or bodily fluids (e.g., bile, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO:136 as residues: Gly-23 to His-30:

          The tissue distribution in osteoclastoma cells indicates that polynucleotides and polypeptides corresponding to this gene are useful for the detection, treatment, and/or prevention of various skeletal system disorders, particularly bone cancer. Moreover, the tissue distribution within the gall bladder indicates that the protein product of this gene is useful for the detection and treatment of liver disorders and cancers (e.g. hepatoblastoma, jaundice, hepatitis, liver metabolic diseases and conditions that are attributable to the differentiation of hepatocyte progenitor cells). In addition the expression in fetus would suggest a useful role for the protein product in developmental abnormalities, fetal deficiencies, pre-natal disorders and various wound-healing models and/or tissue trauma. Osteoclastoma, Gall Bladder tumor. Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:64 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably

excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 979 of SEQ ID NO:64, b is an integer of 15 to 993, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:64, and where the b is greater than or equal to a + 14.

#### FEATURES OF PROTEIN ENCODED BY GENE NO: 55

The translation product of this gene shares sequence homology with b cell growth factor which is thought to be important in B cell development.

10 This gene is expressed primarily in breast lymph node and primary dendritic cells

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, immune disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., cells and tissue of the immune system, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO:137 as residues: Ser-39 to Tyr-46.

20 The tissue distribution combined with its homology to a B-cell growth factor indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and treatment of a variety of immune system disorders. Expression of this gene product in lymph nodes indicates a role in the regulation of the proliferation; survival; differentiation; and/or activation of potentially all hematopoietic cell lineages, including blood stem cells. This gene product may be involved in the regulation of cytokine production, antigen presentation, or other processes that may also suggest a usefulness in the treatment of cancer (e.g. by boosting immune responses). Since the gene is expressed in cells of lymphoid origin, the natural gene product may be involved in immune functions. Therefore it may be also used as an agent for immunological disorders including arthritis, asthma, immune deficiency diseases such as AIDS,

leukemia, rheumatoid arthritis, inflammatory bowel disease, sepsis, acne, and psoriasis. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tumors and tissues. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:65 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 675 of SEQ ID NO:65, b is an integer of 15 to 689, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:65, and where the b is greater than or equal to a + 14.

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 56**

The translation product of this gene shares sequence homology with small hepatocellular oncoprotein which is thought to be important in liver development (See Genebank Accession No. R07057). This gene maps to chromosome 20, and therefore, may be used as a marker in linkage analysis for chromosome 20.

This gene is expressed primarily in monocytes.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, liver disorders, particularly hepatoma. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune and digestive systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., haematopoietic cells and tissue, liver, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level



in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO:138 as residues: Met-17 to Lys-32.

5 The homology to a hepatocellular oncogene indicates that polynucleotides and polypeptides corresponding to this gene are useful for the detection and treatment of liver disorders and cancers (e.g. hepatoblastoma, jaundice, hepatitis, liver metabolic diseases and conditions that are attributable to the differentiation of hepatocyte progenitor cells). The expression also indicates a useful role for the protein product in developmental abnormalities, fetal deficiencies, pre-natal disorders and various wound-healing models and/or tissue trauma. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. Alternatively, The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are . useful for the treatment and diagnosis of hematopoietic related disorders such as anemia, pancytopenia, leukopenia, 15 thrombocytopenia or leukemia since stromal cells are important in the production of cells of hematopoietic lineages. The uses include bone marrow cell ex vivo culture, bone marrow transplantation, bone marrow reconstitution, radiotherapy or chemotherapy of neoplasia. The gene product may also be involved in lymphopoiesis, therefore, it can be used in immune disorders such as infection, inflammation, allergy, 20 immunodeficiency etc. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:66 and may have been publicly available prior to conception of the present invention. Preferably, 25 such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer 30 between 1 to 928 of SEQ ID NO:66, b is an integer of 15 to 942, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:66, and where the b is greater than or equal to a + 14.

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 57**

35 The translation product of this gene was shown to have homology to the human proteins myotubularin related protein 3 and NTII-1 nerve protein (See Genebank

Accession Nos. gill378120 and R99800, respectively) which are both thought to play important roles as growth factors in muscle and nerve tissue, respectively. Preferred polypeptides comprise the following amino acid sequence:

DDDGLPFPTDVIQHRLRQIEAGYKQEVEQLRR

- 5 QVRDSDEXGHPSLLCPSSRAPMDYEDDFTCLKESDGSDDTEDFGSDHSEDCLSEA  
SWEPVDKKETEVTRWVPDHMASHCYNCDCEFWLAKRRHHCRNCGNVFCAG  
CCHLKLPIPDQQLYDPVLVCNSCYXTHSSLSCQGTHEPTAEETHCYSFQLNAGE  
KPVQF (SEQ ID NO:173), SEASWEPVDKKETEVTRWVPDHMASHCY (SEQ ID  
NO:174), HHCRNCGNVF (SEQ ID NO:175, and/or RLRQIEAGYKQEVE (SEQ ID  
10 NO:176). Also preferred are the polynucleotides encoding these polypeptides.

This gene is expressed primarily in bone, spleen, brain, apoptotic T cells, hypothalamus, and other immune cells.

- Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a  
15 biological sample and for diagnosis of diseases and conditions which include, but are not limited to, immune system, musculoskeletal, and neural disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the central nervous  
20 and immune systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., cells and tissue of the immune system, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene  
25 expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO:139 as residues: Glu-63 to Asp-68.

- The tissue distribution in neural tissue combined with the homology to a nerve growth factor indicates that polynucleotides and polypeptides corresponding to this  
30 gene are useful for the detection/treatment of neurodegenerative disease states and behavioral disorders such as Alzheimers Disease, Parkinsons Disease, Huntingtons Disease, Tourette Syndrome, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and  
35 perception, as well as neuromuscular disorders such as MS and muscular dystrophy. In addition, the gene or gene product may also play a role in the treatment and/or detection

of developmental disorders associated with the developing embryo, sexually-linked disorders, or disorders of the cardiovascular system. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:67 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2295 of SEQ ID NO:67, b is an integer of 15 to 2309, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:67, and where the b is greater than or equal to a + 14.

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 58**

This gene is expressed primarily in ovary.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, ovarian cancer, and other disorders that afflict the female reproductive system. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the female reproductive system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., reproductive tissue, and cancerous and wounded tissues) or bodily fluids (e.g., amniotic fluid, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO:140 as residues: Pro-23 to Gly-54.

The tissue distribution in tumors the ovary indicates that polynucleotides and polypeptides corresponding to this gene are useful for diagnosis and intervention of these tumors, in addition to other tumors where expression has been indicated. Protein, as well as, antibodies directed against the protein may show utility as a tissue-specific

marker and/or immunotherapy target for the above listed tissues. Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:68 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 800 of SEQ ID NO:68, b is an integer of 15 to 814, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:68, and where the b is greater than or equal to a + 14.

#### FEATURES OF PROTEIN ENCODED BY GENE NO: 59

This gene is expressed primarily in ovary.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, ovarian cancer, and other disorders afflicting the female reproductive system. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the reproductive system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., reproductive tissue, and cancerous and wounded tissues) or bodily fluids (e.g., amniotic fluid, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in ovarian tissue indicates that polynucleotides and polypeptides corresponding to this gene are useful for diagnosis and intervention of ovarian tumors, in addition to other tumors of the female reproductive system. Protein, as well as, antibodies directed against the protein may show utility as a tissue-specific marker and/or immunotherapy target for the above listed tissues. Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:69 and may have been publicly available prior to conception of the present invention. Preferably,

such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer  
5 between 1 to 774 of SEQ ID NO:69, b is an integer of 15 to 788, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:69, and where the b is greater than or equal to a + 14.

### FEATURES OF PROTEIN ENCODED BY GENE NO: 60

10 When tested against PC12 cell lines, supernatants removed from cells containing this gene activated the EGR1 (early growth response 1) pathway. Thus, it is likely that this gene activates sensory neuronal cells through the EGR1 signal transduction pathway. EGR1 is a separate signal transduction pathway from Jaks-STAT, genes containing the EGR1 promoter are induced in various tissues and cell  
15 types upon activation, leading the cells to undergo differentiation and proliferation.

This gene is expressed primarily in osteoblast.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are  
20 not limited to, skeletal disorders, particular bone cancer. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the Bone, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell  
25 types (e.g., skeletal tissue, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a  
30 sequence shown in SEQ ID NO:142 as residues: Tyr-20 to Lys-31.

In addition the expression of this gene product in synovium would suggest a role in the detection and treatment of disorders and conditions affecting the skeletal system, in particular osteoporosis as well as disorders afflicting connective tissues (e.g. arthritis, trauma, tendonitis, chondromalacia and inflammation) as well as in the  
35 diagnosis or treatment of various autoimmune disorders such as rheumatoid arthritis, lupus, scleroderma, and dermatomyositis as well as dwarfism, spinal deformation,

and specific joint abnormalities as well as chondrodysplasias i.e. spondyloepiphyseal dysplasia congenita, familial osteoarthritis, Atelosteogenesis type II, metaphyseal chondrodysplasia type Schmid. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:70 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 777 of SEQ ID NO:70, b is an integer of 15 to 791, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:70, and where the b is greater than or equal to a + 14.

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 61**

This gene is expressed primarily in adipocyte.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, obesity. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., adipose tissue, and cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO:143 as residues: His-2 to Leu-8.

The tissue distribution would suggest that polynucleotides and polypeptides corresponding to this gene are useful in the diagnosis, treatment, and/or prevention of obesity and lipid metabolism disorders. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. Many polynucleotide sequences, such as EST sequences, are

publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:71 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 790 of SEQ ID NO:71, b is an integer of 15 to 804, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:71, and where the b is greater than or equal to a + 14.

#### FEATURES OF PROTEIN ENCODED BY GENE NO: 62

When tested against Jurkat T-cell lines, supernatants removed from cells containing this gene activated the GAS (gamma activation site) pathway. Thus, it is likely that this gene activates T-cells through the Jak-STAT signal transduction pathway. GAS is a promoter element found upstream in many genes which are involved in the Jaks-STAT pathway. The Jaks-STAT pathway is a large, signal transduction pathway involved in the differentiation and proliferation of cells.

This gene is expressed primarily in synovial tissue.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, chronic synovitis, immune. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., cells and tissue of the immune system, and skeletal tissue, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO:144 as residues: Pro-74 to Lys-82.

The biological assay results indicating activity in Jurkat T-cells for the protein product of this gene indicates that polynucleotides and polypeptides corresponding to this gene useful for the diagnosis and treatment of a variety of immune system

disorders. This gene product may be involved in the regulation of cytokine production, antigen presentation, or other processes that may also suggest a usefulness in the treatment of cancer (e.g. by boosting immune responses). Since the gene has been shown to activate genes in cells of lymphoid origin, the natural gene product may be involved in immune functions. Therefore it may be also used as an agent for immunological disorders including arthritis, asthma, immune deficiency diseases such as AIDS, leukemia, rheumatoid arthritis, inflammatory bowel disease, sepsis, acne, and psoriasis. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tumors and tissues.

In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. In addition the expression of this gene product in synovial tissues indicates a role for this protein in the detection and treatment of disorders and conditions affecting the skeletal system, in particular the connective tissues (e.g. arthritis, trauma, tendonitis, chondromalacia and inflammation) as well as in the diagnosis or treatment of various autoimmune disorders such as rheumatoid arthritis, lupus, scleroderma, and dermatomyositis as well as dwarfism, spinal deformation, and specific joint abnormalities as well as chondrodysplasias i.e. spondyloepiphyseal dysplasia congenita, familial osteoarthritis, Atelosteogenesis type II, metaphyseal chondrodysplasia type Schmid. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. . Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:72 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 769 of SEQ ID NO:72, b is an integer of 15 to 783, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:72, and where the b is greater than or equal to a + 14.

#### FEATURES OF PROTEIN ENCODED BY GENE NO: 63

The translation product of this gene shares sequence homology with fetal troponin which is known to be essential for normal muscular function in all skeletal and cardiovascular muscles.



This gene is expressed primarily in melanocytes, fetal liver, brain, testes, spleen, and placenta.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, melanoma, neuromuscular disorders, such as multiple sclerosis, and endothelial-related diseases. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., muscle, endothelial cells and tissue, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO:145 as residues: Ala-27 to Leu-36, Phe-40 to Leu-50.

The tissue distribution and homology to troponin indicates that polynucleotides and polypeptides corresponding to this gene are useful for treatment, diagnosis, and/or prevention of various neuromuscular disorders such as MS, muscular dystrophy, cardiomyopathy, myositis, myomas, leiomyomas, rhabdomyosarcomas, and coronary heart disease. Alternatively, the expression in a variety of fetal immune tissues indicates that the protein product of this gene is useful for the diagnosis and treatment of a variety of immune system disorders. Expression of this gene product in spleen and fetal liver indicates a role in the regulation of the proliferation; survival; differentiation; and/or activation of potentially all hematopoietic cell lineages, including blood stem cells. This gene product may be involved in the regulation of cytokine production, antigen presentation, or other processes that may also suggest a usefulness in the treatment of cancer (e.g. by boosting immune responses). Since the gene is expressed in cells of lymphoid origin, the natural gene product may be involved in immune functions. Therefore it may be also used as an agent for immunological disorders including arthritis, asthma, immune deficiency diseases such as AIDS, leukemia, rheumatoid arthritis, inflammatory bowel disease, sepsis, acne, and psoriasis. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tumors and tissues. In addition, this

gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

- 5 Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:73 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome.
- 10 Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1509 of SEQ ID NO:73, b is an integer of 15 to 1523, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:73, and where the b is greater than or equal to a + 14.

15

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 64**

The translation product of this gene shares sequence homology with small hepatocellular oncoprotein gene which is thought to be important in liver disorders (See Genbank Accession No. R07057). One embodiment of this gene comprises

- 20 polypeptides of the following amino acid sequence:

MSHCARPLFFETFFILLSPRLKCSGTNTVHYSLLDGLSSNSASVPQVGGLTNAQ  
HDTWLIFVFCVCVCEPLRRPWAAFLISVTSSIK (SEQ ID NO:177), and/or  
VPQVGGLTNAQHDTWLIFVFCVCVCEPLRR (SEQ ID NO:178). An additional  
embodiment is the polynucleotides encoding these polypeptides.

- 25 This gene is expressed primarily in neutrophils, hemangiopericytoma, activated T cells.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are

30 not limited to, immune and hepatic disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the hepatoma and immune system disorder, expression of this gene at significantly higher or lower levels may be routinely detected

35 in certain tissues or cell types (e.g., cells and tissue of the immune system, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine,

synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO:146 as residues: Arg-20 to Gly-25.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and treatment of a variety of immune system disorders. Expression of this gene product in neutrophils and T-cells indicates a role in the regulation of the proliferation; survival; differentiation; and/or activation of potentially all hematopoietic cell lineages, including blood stem cells. This gene product may be involved in the regulation of cytokine production, antigen presentation, or other processes that may also suggest a usefulness in the treatment of cancer (e.g. by boosting immune responses). Since the gene is expressed in cells of lymphoid origin, the natural gene product may be involved in immune functions.

Therefore it may be also used as an agent for immunological disorders including arthritis, asthma, immune deficiency diseases such as AIDS, leukemia, rheumatoid arthritis, inflammatory bowel disease, sepsis, acne, and psoriasis. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tumors and tissues. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Alternatively, the homology to a hepatic oncogene indicates that the protein product of this gene is useful for the detection and treatment of liver disorders and cancers (e.g. hepatoblastoma, jaundice, hepatitis, liver metabolic diseases and conditions that are attributable to the differentiation of hepatocyte progenitor cells). In addition, the expression would suggest a useful role for the protein product in developmental abnormalities, fetal deficiencies, pre-natal disorders and various wound-healing models and/or tissue trauma. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:74 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome.

Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of

a-b, where a is any integer between 1 to 744 of SEQ ID NO:74, b is an integer of 15 to 758, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:74, and where the b is greater than or equal to a + 14.

Gene No.	cDNA Clone ID	ATCC Deposit Nr and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
1	HSXBV35	209138 07/03/97	Uni-ZAP XR	11	558	1	558	106	106	83	1	19	20	47
2	HTEDF42	209138 07/03/97	Uni-ZAP XR	12	715	82	715	115	115	84	1	29	30	37
3	HTGAW51	209138 07/03/97	Uni-ZAP XR	13	838	1	838	41	41	85	1	44	45	52
4	HTLBG08	209138 07/03/97	Uni-ZAP XR	14	513	1	513	117	117	86	1	25	26	25
5	HTLFE42	209138 07/03/97	Uni-ZAP XR	15	712	1	712	116	116	87	1	22	23	77
6	HTSEW17	209138 07/03/97	pBluescript	16	652	1	652	170	170	88	1	35	36	37
7	HTWFK09	209138 07/03/97	pSport1	17	742	1	742	378	378	89	1	18	19	43
8	HTXDJ88	209138 07/03/97	Uni-ZAP XR	18	1219	111	913	162	162	90	1	28	29	59
9	HUSGC54	209138 07/03/97	pSport1	19	874	1	874	148	148	91	1	42	43	54
10	HWTD49	209138 07/03/97	Uni-ZAP XR	20	464	110	464	149	149	92	1	48	49	50
11	HWTBK81	209138 07/03/97	Uni-ZAP XR	21	637	78	635	139	139	93	1	23	24	155
12	HACBH16	209138 07/03/97	Uni-ZAP XR	22	752	1	752	27	27	94	1	37	38	60
13	HCUDE16	209138 07/03/97	ZAP Express	23	492	1	454	104	104	95	1	24	25	70

Gene No.	cDNA Clone ID	ATCC Deposit Nr and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
14	HHEPT60	209138 07/03/97	pCMVSPORT 3.0	24	532	21	532	245	245	96	1	18	19	36
15	HLWBZ73	209138 07/03/97	pCMVSPORT 3.0	25	920	352	905	434	434	97	1	28	29	59
16	HNGFR75	209138 07/03/97	Uni-ZAP XR	26	917	1	917	54	54	98	1	23	24	43
17	HNHEO73	209138 07/03/97	Uni-ZAP XR	27	662	1	662	84	84	99	1	28	29	31
18	HNHFO29	209138 07/03/97	Uni-ZAP XR	28	699	1	699	160	160	100	1	21	22	180
19	HONAH29	209138 07/03/97	pBluescript SK-	29	1637	17	1632	144	144	101	1	25	26	211
20	HGCAB62	209138 07/03/97	pSport1	30	2142	1223	2109	110	110	102	1	47	48	621
20	HGCAB62	209138 07/03/97	pSport1	75	1096	209	1096	406	406	147	1	41	42	230
21	HAQBI01	209138 07/03/97	Uni-ZAP XR	31	1564	1084	1564	231	231	103	1	19	20	287
21	HAQBI01	209138 07/03/97	Uni-ZAP XR	76	1230	406	1171		637	148	1	20	21	62
22	HCMWSW93	209139 07/03/97	Uni-ZAP XR	32	1631	254	855	362	362	104	1	25	26	31
23	HDPBA48	209139 07/03/97	pCMVSPORT 3.0	33	978	1	978	478	478	105	1	48	49	77
23	HDPBA48	209139 07/03/97	pCMVSPORT 3.0	77	911	1	911		309	149	1	12	13	17

Gene No.	cDNA Clone ID	ATCC Deposit Nr and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
24	HE6CT22	209139 07/03/97	Uni-ZAP XR	34	898	1	898	203	203	106	1	22	23	44
25	HE6CT56	209139 07/03/97	Uni-ZAP XR	35	754	9	754	51	51	107	1	17	18	41
26	HE6CY88	209139 07/03/97	Uni-ZAP XR	36	699	1	699	50	50	108	1	16	17	69
27	HE9FT63	209139 07/03/97	Uni-ZAP XR	37	971	322	971	447	447	109	1	41	42	48
28	HE9ND43	209139 07/03/97	Uni-ZAP XR	38	872	19	777	205	205	110	1	25	26	192
29	HERAN63	209139 07/03/97	Uni-ZAP XR	39	608	1	608	394	394	111	1	25	26	71
30	HGLDB64	209139 07/03/97	Uni-ZAP XR	40	855	12	838	245	245	112	1	32	33	35
31	HHBAG14	209139 07/03/97	pCMVSPORT 1	41	1042	1	274	172	172	113	1	24	25	59
32	HJABC16	209139 07/03/97	pBluescript SK-	42	702	1	702	7	7	114	1	25	26	28
33	HKPAD05	209139 07/03/97	Uni-ZAP XR	43	642	52	617	392	392	115	1	19	20	24
34	HKTAE71	209139 07/03/97	Uni-ZAP XR	44	1219	591	1219	646	646	116	1	17	18	34
35	HMADU73	209139 07/03/97	Uni-ZAP XR	45	437	1	437	115	115	117	1	16	17	77
36	HMEAI74	209139 07/03/97	Lambda ZAP II	46	533	1	533	53	53	118	1	20	21	43

Gene No.	cDNA Clone ID	ATCC Deposit Nr and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
37	HPEBT96	209139 07/03/97	Uni-ZAP XR	47	1849	812	1517	968	968	119	1	37	38	45
38	HPFCE63	209139 07/03/97	Uni-ZAP XR	48	926	203	926	414	414	120	1	17	18	28
39	HPMBZ15	209139 07/03/97	Uni-ZAP XR	49	1593	182	1593	1124	1124	121	1	49	50	62
39	HPMBZ15	209139 07/03/97	Uni-ZAP XR	78	488	20	488	121	121	150	1			15
40	HROAE16	209139 07/03/97	Uni-ZAP XR	50	978	1	978	209	209	122	1	32	33	86
41	HSAYM40	209139 07/03/97	Uni-ZAP XR	51	433	1	433	190	190	123	1	19	20	63
42	HSNAD72	209139 07/03/97	Uni-ZAP XR	52	861	1	861	220	220	124	1	22	23	35
43	HSNAU78	209139 07/03/97	Uni-ZAP XR	53	510	1	510	89	89	125	1	17	18	31
44	HTBAB28	209139 07/03/97	Uni-ZAP XR	54	309	1	309	43	43	126	1	35	36	40
45	HALSQ38	209141 07/09/97	Uni-ZAP XR	55	1585	741	1585	776	776	127	1	17	18	27
46	HAQBT52	209141 07/09/97	Uni-ZAP XR	56	874	20	874	136	136	128	1	47	48	68
47	HBIBL04	209141 07/09/97	Uni-ZAP XR	57	1169	5	753	726	726	129	1	40	41	87
47	HBIBL04	209141 07/09/97	Uni-ZAP XR	79	753	1	749	228	228	151	1	21	22	21



Gene No.	cDNA Clone ID	ATCC Deposit Nr and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
48	HBJC195	209141 07/09/97	Uni-ZAP XR	58	1066	1	1066	188	188	130	1	12	13	63
49	HBNBQ61	209141 07/09/97	Uni-ZAP XR	59	772	1	772	88	88	131	1			36
50	HE2ID06	209141 07/09/97	Uni-ZAP XR	60	1198	554	1198	715	715	132	1	28	29	40
51	HEBCM63	209141 07/09/97	Uni-ZAP XR	61	558	1	558	246	246	133	1	26	27	68
52	HFFAK76	209141 07/09/97	Lambda ZAP II	62	616	1	616	150	150	134	1	17	18	47
53	HFRBF28	209141 07/09/97	Uni-ZAP XR	63	811	1	811	57	57	135	1	16	17	16
54	HGBHM89	209141 07/09/97	Uni-ZAP XR	64	993	1	970	49	49	136	1	28	29	54
55	HLMBP18	209141 07/09/97	Lambda ZAP II	65	689	1	689		398	137	1			14
56	HMSEL55	209141 07/09/97	Uni-ZAP XR	66	942	1	942	437	437	138	1	18	19	35
57	HMWCF89	209141 07/09/97	Uni-Zap XR	67	2309	1609	2308	1216	1216	139	1	23	24	80
57	HMWCF89	209141 07/09/97	Uni-Zap XR	80	2138	1435	2138	1467	1467	152	1	22	23	24
58	HODAZ55	209141 07/09/97	Uni-ZAP XR	68	814	1	814	37	37	140	1	16	17	24
59	HODDF08	209141 07/09/97	Uni-ZAP XR	69	788	1	788	141	141	141	1	32	33	50

Gene No.	cDNA Clone ID	ATCC Deposit Nr and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
60	HOSDK95	209141 07/09/97	Uni-ZAP XR	70	791	1	791	121	121	142	1	28	29	29
61	HOUAR65	209141 07/09/97	Uni-ZAP XR	71	804	1	804		53	143	1	28	29	49
62	HSVAC77	209141 07/09/97	Uni-ZAP XR	72	783	1	783	27	27	144	1	28	29	86
63	HJAAT30	209141 07/09/97	pBluescript SK-	73	1523	767	1448	855	855	145	1	23	24	57
63	HJAAT30	209141 07/09/97	pBluescript SK-	81	1327	71	750	386	386	153	1	39	40	40
64	HNECF34	209141 07/09/97	Uni-ZAP XR	74	758	1	758	106	106	146	1	23	24	87
64	HNECF34	209141 07/09/97	Uni-ZAP XR	82	758	1	758	269	269	154	1	17	18	24

Table 1 summarizes the information corresponding to each "Gene No." described above. The nucleotide sequence identified as "NT SEQ ID NO:X" was assembled from partially homologous ("overlapping") sequences obtained from the "cDNA clone ID" identified in Table 1 and, in some cases, from additional related DNA clones. The overlapping sequences were assembled into a single contiguous sequence of high redundancy (usually three to five overlapping sequences at each nucleotide position), resulting in a final sequence identified as SEQ ID NO:X.

The cDNA Clone ID was deposited on the date and given the corresponding deposit number listed in "ATCC Deposit No:Z and Date." Some of the deposits contain multiple different clones corresponding to the same gene. "Vector" refers to the type of vector contained in the cDNA Clone ID.

"Total NT Seq." refers to the total number of nucleotides in the contig identified by "Gene No." The deposited clone may contain all or most of these sequences, reflected by the nucleotide position indicated as "5' NT of Clone Seq." and the "3' NT of Clone Seq." of SEQ ID NO:X. The nucleotide position of SEQ ID NO:X of the putative start codon (methionine) is identified as "5' NT of Start Codon." Similarly, the nucleotide position of SEQ ID NO:X of the predicted signal sequence is identified as "5' NT of First AA of Signal Pep."

The translated amino acid sequence, beginning with the methionine, is identified as "AA SEQ ID NO:Y," although other reading frames can also be easily translated using known molecular biology techniques. The polypeptides produced by these alternative open reading frames are specifically contemplated by the present invention.

The first and last amino acid position of SEQ ID NO:Y of the predicted signal peptide is identified as "First AA of Sig Pep" and "Last AA of Sig Pep." The predicted first amino acid position of SEQ ID NO:Y of the secreted portion is identified as "Predicted First AA of Secreted Portion." Finally, the amino acid position of SEQ ID NO:Y of the last amino acid in the open reading frame is identified as "Last AA of ORF."

SEQ ID NO:X and the translated SEQ ID NO:Y are sufficiently accurate and otherwise suitable for a variety of uses well known in the art and described further below. For instance, SEQ ID NO:X is useful for designing nucleic acid hybridization probes that will detect nucleic acid sequences contained in SEQ ID NO:X or the cDNA contained in the deposited clone. These probes will also hybridize to nucleic acid molecules in biological samples, thereby enabling a variety of forensic and diagnostic methods of the invention. Similarly, polypeptides identified from SEQ ID NO:Y may be used to generate antibodies which bind specifically to the secreted proteins encoded by the cDNA clones identified in Table 1.

Nevertheless, DNA sequences generated by sequencing reactions can contain sequencing errors. The errors exist as misidentified nucleotides, or as insertions or deletions of nucleotides in the generated DNA sequence. The erroneously inserted or deleted nucleotides cause frame shifts in the reading frames of the predicted amino acid sequence. In these cases, the predicted amino acid sequence diverges from the actual amino acid sequence, even though the generated DNA sequence may be greater than 99.9% identical to the actual DNA sequence (for example, one base insertion or deletion in an open reading frame of over 1000 bases).

Accordingly, for those applications requiring precision in the nucleotide sequence or the amino acid sequence, the present invention provides not only the generated nucleotide sequence identified as SEQ ID NO:X and the predicted translated amino acid sequence identified as SEQ ID NO:Y, but also a sample of plasmid DNA containing a human cDNA of the invention deposited with the ATCC, as set forth in Table 1. The nucleotide sequence of each deposited clone can readily be determined by sequencing the deposited clone in accordance with known methods. The predicted amino acid sequence can then be verified from such deposits. Moreover, the amino acid sequence of the protein encoded by a particular clone can also be directly determined by peptide sequencing or by expressing the protein in a suitable host cell containing the deposited human cDNA, collecting the protein, and determining its sequence.

The present invention also relates to the genes corresponding to SEQ ID NO:X, SEQ ID NO:Y, or the deposited clone. The corresponding gene can be isolated in accordance with known methods using the sequence information disclosed herein. Such methods include preparing probes or primers from the disclosed sequence and identifying or amplifying the corresponding gene from appropriate sources of genomic material.

Also provided in the present invention are species homologs. Species homologs may be isolated and identified by making suitable probes or primers from the sequences provided herein and screening a suitable nucleic acid source for the desired homolog.

The polypeptides of the invention can be prepared in any suitable manner. Such polypeptides include isolated naturally occurring polypeptides, recombinantly produced polypeptides, synthetically produced polypeptides, or polypeptides produced by a combination of these methods. Means for preparing such polypeptides are well understood in the art.

The polypeptides may be in the form of the secreted protein, including the mature form, or may be a part of a larger protein, such as a fusion protein (see below).

It is often advantageous to include an additional amino acid sequence which contains secretory or leader sequences, pro-sequences, sequences which aid in purification, such as multiple histidine residues, or an additional sequence for stability during recombinant production.

- 5       The polypeptides of the present invention are preferably provided in an isolated form, and preferably are substantially purified. A recombinantly produced version of a polypeptide, including the secreted polypeptide, can be substantially purified by the one-step method described in Smith and Johnson, *Gene* 67:31-40 (1988). Polypeptides of the invention also can be purified from natural or recombinant sources  
10       using antibodies of the invention raised against the secreted protein in methods which are well known in the art.

### Signal Sequences

- 15       Methods for predicting whether a protein has a signal sequence, as well as the cleavage point for that sequence, are available. For instance, the method of McGeoch, *Virus Res.* 3:271-286 (1985), uses the information from a short N-terminal charged region and a subsequent uncharged region of the complete (uncleaved) protein. The method of von Heinje, *Nucleic Acids Res.* 14:4683-4690 (1986) uses the information  
20       from the residues surrounding the cleavage site, typically residues -13 to +2, where +1 indicates the amino terminus of the secreted protein. The accuracy of predicting the cleavage points of known mammalian secretory proteins for each of these methods is in the range of 75-80%. (von Heinje, *supra*.) However, the two methods do not always produce the same predicted cleavage point(s) for a given protein.

- 25       In the present case, the deduced amino acid sequence of the secreted polypeptide was analyzed by a computer program called SignalP (Henrik Nielsen et al., *Protein Engineering* 10:1-6 (1997)), which predicts the cellular location of a protein based on the amino acid sequence. As part of this computational prediction of localization, the methods of McGeoch and von Heinje are incorporated. The analysis of the amino acid sequences of the secreted proteins described herein by this program provided the results  
30       shown in Table 1.

- 35       As one of ordinary skill would appreciate, however, cleavage sites sometimes vary from organism to organism and cannot be predicted with absolute certainty. Accordingly, the present invention provides secreted polypeptides having a sequence shown in SEQ ID NO:Y which have an N-terminus beginning within 5 residues (i.e., + or - 5 residues) of the predicted cleavage point. Similarly, it is also recognized that in some cases, cleavage of the signal sequence from a secreted protein is not entirely

uniform, resulting in more than one secreted species. These polypeptides, and the polynucleotides encoding such polypeptides, are contemplated by the present invention.

Moreover, the signal sequence identified by the above analysis may not necessarily predict the naturally occurring signal sequence. For example, the naturally occurring signal sequence may be further upstream from the predicted signal sequence. However, it is likely that the predicted signal sequence will be capable of directing the secreted protein to the ER. These polypeptides, and the polynucleotides encoding such polypeptides, are contemplated by the present invention.

### 10 Polynucleotide and Polypeptide Variants

"Variant" refers to a polynucleotide or polypeptide differing from the polynucleotide or polypeptide of the present invention, but retaining essential properties thereof. Generally, variants are overall closely similar, and, in many regions, identical to the polynucleotide or polypeptide of the present invention.

15 By a polynucleotide having a nucleotide sequence at least, for example, 95% "identical" to a reference nucleotide sequence of the present invention, it is intended that the nucleotide sequence of the polynucleotide is identical to the reference sequence except that the polynucleotide sequence may include up to five point mutations per each 100 nucleotides of the reference nucleotide sequence encoding the polypeptide. In other words, to obtain a polynucleotide having a nucleotide sequence at least 95% identical to a reference nucleotide sequence, up to 5% of the nucleotides in the reference sequence may be deleted or substituted with another nucleotide, or a number of nucleotides up to 5% of the total nucleotides in the reference sequence may be inserted into the reference sequence. The query sequence may be an entire sequence shown in Table 1, the ORF (open reading frame), or any fragment specified as described herein.

25 As a practical matter, whether any particular nucleic acid molecule or polypeptide is at least 90%, 95%, 96%, 97%, 98% or 99% identical to a nucleotide sequence of the present invention can be determined conventionally using known computer programs. A preferred method for determining the best overall match between a query sequence (a sequence of the present invention) and a subject sequence, also referred to as a global sequence alignment, can be determined using the FASTDB computer program based on the algorithm of Brutlag et al. (Comp. App. Biosci. (1990) 6:237-245). In a sequence alignment the query and subject sequences are both DNA sequences. An RNA sequence can be compared by converting U's to T's. The result of said global sequence alignment is in percent identity. Preferred parameters used in a FASTDB alignment of DNA sequences to calculate percent identity are:

35 Matrix=Unitary, k-tuple=4, Mismatch Penalty=1, Joining Penalty=30, Randomization

Group Length=0, Cutoff Score=1, Gap Penalty=5, Gap Size Penalty 0.05, Window Size=500 or the length of the subject nucleotide sequence, whichever is shorter.

If the subject sequence is shorter than the query sequence because of 5' or 3' deletions, not because of internal deletions, a manual correction must be made to the results. This is because the FASTDB program does not account for 5' and 3' truncations of the subject sequence when calculating percent identity. For subject sequences truncated at the 5' or 3' ends, relative to the query sequence, the percent identity is corrected by calculating the number of bases of the query sequence that are 5' and 3' of the subject sequence, which are not matched/aligned, as a percent of the total bases of the query sequence. Whether a nucleotide is matched/aligned is determined by results of the FASTDB sequence alignment. This percentage is then subtracted from the percent identity, calculated by the above FASTDB program using the specified parameters, to arrive at a final percent identity score. This corrected score is what is used for the purposes of the present invention. Only bases outside the 5' and 3' bases of the subject sequence, as displayed by the FASTDB alignment, which are not matched/aligned with the query sequence, are calculated for the purposes of manually adjusting the percent identity score.

For example, a 90 base subject sequence is aligned to a 100 base query sequence to determine percent identity. The deletions occur at the 5' end of the subject sequence and therefore, the FASTDB alignment does not show a matched/alignment of the first 10 bases at 5' end. The 10 unpaired bases represent 10% of the sequence (number of bases at the 5' and 3' ends not matched/total number of bases in the query sequence) so 10% is subtracted from the percent identity score calculated by the FASTDB program. If the remaining 90 bases were perfectly matched the final percent identity would be 90%. In another example, a 90 base subject sequence is compared with a 100 base query sequence. This time the deletions are internal deletions so that there are no bases on the 5' or 3' of the subject sequence which are not matched/aligned with the query. In this case the percent identity calculated by FASTDB is not manually corrected. Once again, only bases 5' and 3' of the subject sequence which are not matched/aligned with the query sequence are manually corrected for. No other manual corrections are to be made for the purposes of the present invention.

By a polypeptide having an amino acid sequence at least, for example, 95% "identical" to a query amino acid sequence of the present invention, it is intended that the amino acid sequence of the subject polypeptide is identical to the query sequence except that the subject polypeptide sequence may include up to five amino acid alterations per each 100 amino acids of the query amino acid sequence. In other words, to obtain a polypeptide having an amino acid sequence at least 95% identical to a query

amino acid sequence, up to 5% of the amino acid residues in the subject sequence may be inserted, deleted, (indels) or substituted with another amino acid. These alterations of the reference sequence may occur at the amino or carboxy terminal positions of the reference amino acid sequence or anywhere between those terminal positions,

5 interspersed either individually among residues in the reference sequence or in one or more contiguous groups within the reference sequence.

As a practical matter, whether any particular polypeptide is at least 90%, 95%, 96%, 97%, 98% or 99% identical to, for instance, the amino acid sequences shown in Table 1 or to the amino acid sequence encoded by deposited DNA clone can be  
10 determined conventionally using known computer programs. A preferred method for determining the best overall match between a query sequence (a sequence of the present invention) and a subject sequence, also referred to as a global sequence alignment, can be determined using the FASTDB computer program based on the algorithm of Brutlag et al. (Comp. App. Biosci. (1990) 6:237-245). In a sequence alignment the query and  
15 subject sequences are either both nucleotide sequences or both amino acid sequences. The result of said global sequence alignment is in percent identity. Preferred parameters used in a FASTDB amino acid alignment are: Matrix=PAM 0, k-tuple=2, Mismatch Penalty=1, Joining Penalty=20, Randomization Group Length=0, Cutoff Score=1, Window Size=sequence length, Gap Penalty=5, Gap Size Penalty=0.05, Window  
20 Size=500 or the length of the subject amino acid sequence, whichever is shorter.

If the subject sequence is shorter than the query sequence due to N- or C-terminal deletions, not because of internal deletions, a manual correction must be made to the results. This is because the FASTDB program does not account for N- and C-terminal truncations of the subject sequence when calculating global percent identity.  
25 For subject sequences truncated at the N- and C-termini, relative to the the query sequence, the percent identity is corrected by calculating the number of residues of the query sequence that are N- and C-terminal of the subject sequence, which are not matched/aligned with a corresponding subject residue, as a percent of the total bases of the query sequence. Whether a residue is matched/aligned is determined by results of  
30 the FASTDB sequence alignment. This percentage is then subtracted from the percent identity, calculated by the above FASTDB program using the specified parameters, to arrive at a final percent identity score. This final percent identity score is what is used for the purposes of the present invention. Only residues to the N- and C-termini of the subject sequence, which are not matched/aligned with the query sequence, are  
35 considered for the purposes of manually adjusting the percent identity score. That is, only query residue positions outside the farthest N- and C-terminal residues of the subject sequence.



For example, a 90 amino acid residue subject sequence is aligned with a 100 residue query sequence to determine percent identity. The deletion occurs at the N-terminus of the subject sequence and therefore, the FASTDB alignment does not show a matching/alignment of the first 10 residues at the N-terminus. The 10 unpaired  
5 residues represent 10% of the sequence (number of residues at the N- and C- termini not matched/total number of residues in the query sequence) so 10% is subtracted from the percent identity score calculated by the FASTDB program. If the remaining 90 residues were perfectly matched the final percent identity would be 90%. In another example, a 90 residue subject sequence is compared with a 100 residue query sequence.  
10 This time the deletions are internal deletions so there are no residues at the N- or C-termini of the subject sequence which are not matched/aligned with the query. In this case the percent identity calculated by FASTDB is not manually corrected. Once again, only residue positions outside the N- and C-terminal ends of the subject sequence, as displayed in the FASTDB alignment, which are not matched/aligned with the query  
15 sequence are manually corrected for. No other manual corrections are to made for the purposes of the present invention.

The variants may contain alterations in the coding regions, non-coding regions, or both. Especially preferred are polynucleotide variants containing alterations which produce silent substitutions, additions, or deletions, but do not alter the properties or  
20 activities of the encoded polypeptide. Nucleotide variants produced by silent substitutions due to the degeneracy of the genetic code are preferred. Moreover, variants in which 5-10, 1-5, or 1-2 amino acids are substituted, deleted, or added in any combination are also preferred. Polynucleotide variants can be produced for a variety of reasons, e.g., to optimize codon expression for a particular host (change codons in  
25 the human mRNA to those preferred by a bacterial host such as *E. coli*).

Naturally occurring variants are called "allelic variants," and refer to one of several alternate forms of a gene occupying a given locus on a chromosome of an organism. (Genes II, Lewin, B., ed., John Wiley & Sons, New York (1985).) These allelic variants can vary at either the polynucleotide and/or polypeptide level.  
30 Alternatively, non-naturally occurring variants may be produced by mutagenesis techniques or by direct synthesis.

Using known methods of protein engineering and recombinant DNA technology, variants may be generated to improve or alter the characteristics of the polypeptides of the present invention. For instance, one or more amino acids can be  
35 deleted from the N-terminus or C-terminus of the secreted protein without substantial loss of biological function. The authors of Ron et al., *J. Biol. Chem.* 268: 2984-2988 (1993), reported variant KGF proteins having heparin binding activity even after

deleting 3, 8, or 27 amino-terminal amino acid residues. Similarly, Interferon gamma exhibited up to ten times higher activity after deleting 8-10 amino acid residues from the carboxy terminus of this protein. (Dobeli et al., J. Biotechnology 7:199-216 (1988).)

Moreover, ample evidence demonstrates that variants often retain a biological activity similar to that of the naturally occurring protein. For example, Gayle and coworkers (J. Biol. Chem 268:22105-22111 (1993)) conducted extensive mutational analysis of human cytokine IL-1a. They used random mutagenesis to generate over 3,500 individual IL-1a mutants that averaged 2.5 amino acid changes per variant over the entire length of the molecule. Multiple mutations were examined at every possible amino acid position. The investigators found that "[m]ost of the molecule could be altered with little effect on either [binding or biological activity]." (See, Abstract.) In fact, only 23 unique amino acid sequences, out of more than 3,500 nucleotide sequences examined, produced a protein that significantly differed in activity from wild-type.

Furthermore, even if deleting one or more amino acids from the N-terminus or C-terminus of a polypeptide results in modification or loss of one or more biological functions, other biological activities may still be retained. For example, the ability of a deletion variant to induce and/or to bind antibodies which recognize the secreted form will likely be retained when less than the majority of the residues of the secreted form are removed from the N-terminus or C-terminus. Whether a particular polypeptide lacking N- or C-terminal residues of a protein retains such immunogenic activities can readily be determined by routine methods described herein and otherwise known in the art.

Thus, the invention further includes polypeptide variants which show substantial biological activity. Such variants include deletions, insertions, inversions, repeats, and substitutions selected according to general rules known in the art so as have little effect on activity. For example, guidance concerning how to make phenotypically silent amino acid substitutions is provided in Bowie, J. U. et al., Science 247:1306-1310 (1990), wherein the authors indicate that there are two main strategies for studying the tolerance of an amino acid sequence to change.

The first strategy exploits the tolerance of amino acid substitutions by natural selection during the process of evolution. By comparing amino acid sequences in different species, conserved amino acids can be identified. These conserved amino acids are likely important for protein function. In contrast, the amino acid positions where substitutions have been tolerated by natural selection indicates that these positions are not critical for protein function. Thus, positions tolerating amino acid substitution could be modified while still maintaining biological activity of the protein.

The second strategy uses genetic engineering to introduce amino acid changes at specific positions of a cloned gene to identify regions critical for protein function. For example, site directed mutagenesis or alanine-scanning mutagenesis (introduction of single alanine mutations at every residue in the molecule) can be used. (Cunningham and Wells, Science 244:1081-1085 (1989).) The resulting mutant molecules can then be tested for biological activity.

As the authors state, these two strategies have revealed that proteins are surprisingly tolerant of amino acid substitutions. The authors further indicate which amino acid changes are likely to be permissive at certain amino acid positions in the protein. For example, most buried (within the tertiary structure of the protein) amino acid residues require nonpolar side chains, whereas few features of surface side chains are generally conserved. Moreover, tolerated conservative amino acid substitutions involve replacement of the aliphatic or hydrophobic amino acids Ala, Val, Leu and Ile; replacement of the hydroxyl residues Ser and Thr; replacement of the acidic residues Asp and Glu; replacement of the amide residues Asn and Gln, replacement of the basic residues Lys, Arg, and His; replacement of the aromatic residues Phe, Tyr, and Trp, and replacement of the small-sized amino acids Ala, Ser, Thr, Met, and Gly.

Besides conservative amino acid substitution, variants of the present invention include (i) substitutions with one or more of the non-conserved amino acid residues, where the substituted amino acid residues may or may not be one encoded by the genetic code, or (ii) substitution with one or more of amino acid residues having a substituent group, or (iii) fusion of the mature polypeptide with another compound, such as a compound to increase the stability and/or solubility of the polypeptide (for example, polyethylene glycol), or (iv) fusion of the polypeptide with additional amino acids, such as an IgG Fc fusion region peptide; or leader or secretory sequence, or a sequence facilitating purification. Such variant polypeptides are deemed to be within the scope of those skilled in the art from the teachings herein.

For example, polypeptide variants containing amino acid substitutions of charged amino acids with other charged or neutral amino acids may produce proteins with improved characteristics, such as less aggregation. Aggregation of pharmaceutical formulations both reduces activity and increases clearance due to the aggregate's immunogenic activity. (Pinckard et al., Clin. Exp. Immunol. 2:331-340 (1967); Robbins et al., Diabetes 36: 838-845 (1987); Cleland et al., Crit. Rev. Therapeutic Drug Carrier Systems 10:307-377 (1993).)

### Polynucleotide and Polypeptide Fragments

In the present invention, a "polynucleotide fragment" refers to a short polynucleotide having a nucleic acid sequence contained in the deposited clone or shown in SEQ ID NO:X. The short nucleotide fragments are preferably at least about 15 nt, and more preferably at least about 20 nt, still more preferably at least about 30 nt, and even more preferably, at least about 40 nt in length. A fragment "at least 20 nt in length," for example, is intended to include 20 or more contiguous bases from the cDNA sequence contained in the deposited clone or the nucleotide sequence shown in SEQ ID NO:X. These nucleotide fragments are useful as diagnostic probes and primers as discussed herein. Of course, larger fragments (e.g., 50, 150, 500, 600, 2000 nucleotides) are preferred.

Moreover, representative examples of polynucleotide fragments of the invention, include, for example, fragments having a sequence from about nucleotide number 1-50, 51-100, 101-150, 151-200, 201-250, 251-300, 301-350, 351-400, 401-450, 451-500, 501-550, 551-600, 651-700, 701-750, 751-800, 800-850, 851-900, 901-950, 951-1000, 1001-1050, 1051-1100, 1101-1150, 1151-1200, 1201-1250, 1251-1300, 1301-1350, 1351-1400, 1401-1450, 1451-1500, 1501-1550, 1551-1600, 1601-1650, 1651-1700, 1701-1750, 1751-1800, 1801-1850, 1851-1900, 1901-1950, 1951-2000, or 2001 to the end of SEQ ID NO:X or the cDNA contained in the deposited clone. In this context "about" includes the particularly recited ranges, larger or smaller by several (5, 4, 3, 2, or 1) nucleotides, at either terminus or at both termini. Preferably, these fragments encode a polypeptide which has biological activity. More preferably, these polynucleotides can be used as probes or primers as discussed herein.

In the present invention, a "polypeptide fragment" refers to a short amino acid sequence contained in SEQ ID NO:Y or encoded by the cDNA contained in the deposited clone. Protein fragments may be "free-standing," or comprised within a larger polypeptide of which the fragment forms a part or region, most preferably as a single continuous region. Representative examples of polypeptide fragments of the invention, include, for example, fragments from about amino acid number 1-20, 21-40, 41-60, 61-80, 81-100, 102-120, 121-140, 141-160, or 161 to the end of the coding region. Moreover, polypeptide fragments can be about 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 130, 140, or 150 amino acids in length. In this context "about" includes the particularly recited ranges, larger or smaller by several (5, 4, 3, 2, or 1) amino acids, at either extreme or at both extremes.

Preferred polypeptide fragments include the secreted protein as well as the mature form. Further preferred polypeptide fragments include the secreted protein or the mature form having a continuous series of deleted residues from the amino or the carboxy terminus, or both. For example, any number of amino acids, ranging from 1-

60, can be deleted from the amino terminus of either the secreted polypeptide or the mature form. Similarly, any number of amino acids, ranging from 1-30, can be deleted from the carboxy terminus of the secreted protein or mature form. Furthermore, any combination of the above amino and carboxy terminus deletions are preferred.

- 5 Similarly, polynucleotide fragments encoding these polypeptide fragments are also preferred.

Particularly, N-terminal deletions of the polypeptide of the present invention can be described by the general formula m-p, where p is the total number of amino acids in the polypeptide and m is an integer from 2 to (p-1), and where both of these integers (m  
10 & p) correspond to the position of the amino acid residue identified in SEQ ID NO:Y.

Moreover, C-terminal deletions of the polypeptide of the present invention can also be described by the general formula 1-n, where n is an integer from 2 to (p-1), and again where these integers (n & p) correspond to the position of the amino acid residue identified in SEQ ID NO:Y.

- 15 The invention also provides polypeptides having one or more amino acids deleted from both the amino and the carboxyl termini, which may be described generally as having residues m-n of SEQ ID NO:Y, where m and n are integers as described above.

Also preferred are polypeptide and polynucleotide fragments characterized by  
20 structural or functional domains, such as fragments that comprise alpha-helix and alpha-helix forming regions, beta-sheet and beta-sheet-forming regions, turn and turn-forming regions, coil and coil-forming regions, hydrophilic regions, hydrophobic regions, alpha amphipathic regions, beta amphipathic regions, flexible regions, surface-forming regions, substrate binding region, and high antigenic index regions.

- 25 Polypeptide fragments of SEQ ID NO:Y falling within conserved domains are specifically contemplated by the present invention. Moreover, polynucleotide fragments encoding these domains are also contemplated.

Other preferred fragments are biologically active fragments. Biologically active fragments are those exhibiting activity similar, but not necessarily identical, to an  
30 activity of the polypeptide of the present invention. The biological activity of the fragments may include an improved desired activity, or a decreased undesirable activity.

### **Epitopes & Antibodies**

- 35 In the present invention, "epitopes" refer to polypeptide fragments having antigenic or immunogenic activity in an animal, especially in a human. A preferred embodiment of the present invention relates to a polypeptide fragment comprising an epitope, as well as the polynucleotide encoding this fragment. A region of a protein

molecule to which an antibody can bind is defined as an "antigenic epitope." In contrast, an "immunogenic epitope" is defined as a part of a protein that elicits an antibody response. (See, for instance, Geysen et al., Proc. Natl. Acad. Sci. USA 81:3998-4002 (1983).)

5           Fragments which function as epitopes may be produced by any conventional means. (See, e.g., Houghten, R. A., Proc. Natl. Acad. Sci. USA 82:5131-5135 (1985) further described in U.S. Patent No. 4,631,211.)

          In the present invention, antigenic epitopes preferably contain a sequence of at least seven, more preferably at least nine, and most preferably between about 15 to  
10       about 30 amino acids. Antigenic epitopes are useful to raise antibodies, including monoclonal antibodies, that specifically bind the epitope. (See, for instance, Wilson et al., Cell 37:767-778 (1984); Sutcliffe, J. G. et al., Science 219:660-666 (1983).)

          Similarly, immunogenic epitopes can be used to induce antibodies according to methods well known in the art. (See, for instance, Sutcliffe et al., supra; Wilson et al.,  
15       supra; Chow, M. et al., Proc. Natl. Acad. Sci. USA 82:910-914; and Bittle, F. J. et al., J. Gen. Virol. 66:2347-2354 (1985).) A preferred immunogenic epitope includes the secreted protein. The immunogenic epitopes may be presented together with a carrier protein, such as an albumin, to an animal system (such as rabbit or mouse) or, if it is long enough (at least about 25 amino acids), without a carrier. However,  
20       immunogenic epitopes comprising as few as 8 to 10 amino acids have been shown to be sufficient to raise antibodies capable of binding to, at the very least, linear epitopes in a denatured polypeptide (e.g., in Western blotting.)

          As used herein, the term "antibody" (Ab) or "monoclonal antibody" (Mab) is meant to include intact molecules as well as antibody fragments (such as, for example,  
25       Fab and F(ab')<sub>2</sub> fragments) which are capable of specifically binding to protein. Fab and F(ab')<sub>2</sub> fragments lack the Fc fragment of intact antibody, clear more rapidly from the circulation, and may have less non-specific tissue binding than an intact antibody. (Wahl et al., J. Nucl. Med. 24:316-325 (1983).) Thus, these fragments are preferred, as well as the products of a FAB or other immunoglobulin expression library.  
30       Moreover, antibodies of the present invention include chimeric, single chain, and humanized antibodies.

### **Fusion Proteins**

          Any polypeptide of the present invention can be used to generate fusion  
35       proteins. For example, the polypeptide of the present invention, when fused to a second protein, can be used as an antigenic tag. Antibodies raised against the polypeptide of the present invention can be used to indirectly detect the second protein

by binding to the polypeptide. Moreover, because secreted proteins target cellular locations based on trafficking signals, the polypeptides of the present invention can be used as targeting molecules once fused to other proteins.

5 Examples of domains that can be fused to polypeptides of the present invention include not only heterologous signal sequences, but also other heterologous functional regions. The fusion does not necessarily need to be direct, but may occur through linker sequences.

Moreover, fusion proteins may also be engineered to improve characteristics of the polypeptide of the present invention. For instance, a region of additional amino  
10 acids, particularly charged amino acids, may be added to the N-terminus of the polypeptide to improve stability and persistence during purification from the host cell or subsequent handling and storage. Also, peptide moieties may be added to the polypeptide to facilitate purification. Such regions may be removed prior to final preparation of the polypeptide. The addition of peptide moieties to facilitate handling of  
15 polypeptides are familiar and routine techniques in the art.

Moreover, polypeptides of the present invention, including fragments, and specifically epitopes, can be combined with parts of the constant domain of immunoglobulins (IgG), resulting in chimeric polypeptides. These fusion proteins facilitate purification and show an increased half-life in vivo. One reported example  
20 describes chimeric proteins consisting of the first two domains of the human CD4-polypeptide and various domains of the constant regions of the heavy or light chains of mammalian immunoglobulins. (EP A 394,827; Traunecker et al., Nature 331:84-86 (1988).) Fusion proteins having disulfide-linked dimeric structures (due to the IgG) can also be more efficient in binding and neutralizing other molecules, than the  
25 monomeric secreted protein or protein fragment alone. (Fountoulakis et al., J. Biochem. 270:3958-3964 (1995).)

Similarly, EP-A-O 464 533 (Canadian counterpart 2045869) discloses fusion proteins comprising various portions of constant region of immunoglobulin molecules together with another human protein or part thereof. In many cases, the Fc part in a  
30 fusion protein is beneficial in therapy and diagnosis, and thus can result in, for example, improved pharmacokinetic properties. (EP-A 0232 262.) Alternatively, deleting the Fc part after the fusion protein has been expressed, detected, and purified, would be desired. For example, the Fc portion may hinder therapy and diagnosis if the fusion protein is used as an antigen for immunizations. In drug discovery, for  
35 example, human proteins, such as hIL-5, have been fused with Fc portions for the purpose of high-throughput screening assays to identify antagonists of hIL-5. (See, D.

Bennett et al., J. Molecular Recognition 8:52-58 (1995); K. Johanson et al., J. Biol. Chem. 270:9459-9471 (1995).)

Moreover, the polypeptides of the present invention can be fused to marker sequences, such as a peptide which facilitates purification of the fused polypeptide. In preferred embodiments, the marker amino acid sequence is a hexa-histidine peptide, such as the tag provided in a pQE vector (QIAGEN, Inc., 9259 Eton Avenue, Chatsworth, CA, 91311), among others, many of which are commercially available. As described in Gentz et al., Proc. Natl. Acad. Sci. USA 86:821-824 (1989), for instance, hexa-histidine provides for convenient purification of the fusion protein. Another peptide tag useful for purification, the "HA" tag, corresponds to an epitope derived from the influenza hemagglutinin protein. (Wilson et al., Cell 37:767 (1984).)

Thus, any of these above fusions can be engineered using the polynucleotides or the polypeptides of the present invention.

#### **Vectors, Host Cells, and Protein Production**

The present invention also relates to vectors containing the polynucleotide of the present invention, host cells, and the production of polypeptides by recombinant techniques. The vector may be, for example, a phage, plasmid, viral, or retroviral vector. Retroviral vectors may be replication competent or replication defective. In the latter case, viral propagation generally will occur only in complementing host cells.

The polynucleotides may be joined to a vector containing a selectable marker for propagation in a host. Generally, a plasmid vector is introduced in a precipitate, such as a calcium phosphate precipitate, or in a complex with a charged lipid. If the vector is a virus, it may be packaged in vitro using an appropriate packaging cell line and then transduced into host cells.

The polynucleotide insert should be operatively linked to an appropriate promoter, such as the phage lambda PL promoter, the E. coli lac, trp, phoA and tac promoters, the SV40 early and late promoters and promoters of retroviral LTRs, to name a few. Other suitable promoters will be known to the skilled artisan. The expression constructs will further contain sites for transcription initiation, termination, and, in the transcribed region, a ribosome binding site for translation. The coding portion of the transcripts expressed by the constructs will preferably include a translation initiating codon at the beginning and a termination codon (UAA, UGA or UAG) appropriately positioned at the end of the polypeptide to be translated.

As indicated, the expression vectors will preferably include at least one selectable marker. Such markers include dihydrofolate reductase, G418 or neomycin resistance for eukaryotic cell culture and tetracycline, kanamycin or ampicillin resistance



genes for culturing in *E. coli* and other bacteria. Representative examples of appropriate hosts include, but are not limited to, bacterial cells, such as *E. coli*, *Streptomyces* and *Salmonella typhimurium* cells; fungal cells, such as yeast cells; insect cells such as *Drosophila* S2 and *Spodoptera* Sf9 cells; animal cells such as CHO, COS, 293, and Bowes melanoma cells; and plant cells. Appropriate culture mediums and conditions for the above-described host cells are known in the art.

Among vectors preferred for use in bacteria include pQE70, pQE60 and pQE-9, available from QIAGEN, Inc.; pBluescript vectors, Phagescript vectors, pNH8A, pNH16a, pNH18A, pNH46A, available from Stratagene Cloning Systems, Inc.; and ptrc99a, pKK223-3, pKK233-3, pDR540, pRIT5 available from Pharmacia Biotech, Inc. Among preferred eukaryotic vectors are pWLNEO, pSV2CAT, pOG44, pXT1 and pSG available from Stratagene; and pSVK3, pBPV, pMSG and pSVL available from Pharmacia. Other suitable vectors will be readily apparent to the skilled artisan.

Introduction of the construct into the host cell can be effected by calcium phosphate transfection, DEAE-dextran mediated transfection, cationic lipid-mediated transfection, electroporation, transduction, infection, or other methods. Such methods are described in many standard laboratory manuals, such as Davis et al., *Basic Methods In Molecular Biology* (1986). It is specifically contemplated that the polypeptides of the present invention may in fact be expressed by a host cell lacking a recombinant vector.

A polypeptide of this invention can be recovered and purified from recombinant cell cultures by well-known methods including ammonium sulfate or ethanol precipitation, acid extraction, anion or cation exchange chromatography, phosphocellulose chromatography, hydrophobic interaction chromatography, affinity chromatography, hydroxylapatite chromatography and lectin chromatography. Most preferably, high performance liquid chromatography ("HPLC") is employed for purification.

Polypeptides of the present invention, and preferably the secreted form, can also be recovered from: products purified from natural sources, including bodily fluids, tissues and cells, whether directly isolated or cultured; products of chemical synthetic procedures; and products produced by recombinant techniques from a prokaryotic or eukaryotic host, including, for example, bacterial, yeast, higher plant, insect, and mammalian cells. Depending upon the host employed in a recombinant production procedure, the polypeptides of the present invention may be glycosylated or may be non-glycosylated. In addition, polypeptides of the invention may also include an initial modified methionine residue, in some cases as a result of host-mediated processes. Thus, it is well known in the art that the N-terminal methionine encoded by the translation initiation codon generally is removed with high efficiency from any protein

after translation in all eukaryotic cells. While the N-terminal methionine on most proteins also is efficiently removed in most prokaryotes, for some proteins, this prokaryotic removal process is inefficient, depending on the nature of the amino acid to which the N-terminal methionine is covalently linked.

5

### Uses of the Polynucleotides

Each of the polynucleotides identified herein can be used in numerous ways as reagents. The following description should be considered exemplary and utilizes known techniques.

10

The polynucleotides of the present invention are useful for chromosome identification. There exists an ongoing need to identify new chromosome markers, since few chromosome marking reagents, based on actual sequence data (repeat polymorphisms), are presently available. Each polynucleotide of the present invention can be used as a chromosome marker.

15

Briefly, sequences can be mapped to chromosomes by preparing PCR primers (preferably 15-25 bp) from the sequences shown in SEQ ID NO:X. Primers can be selected using computer analysis so that primers do not span more than one predicted exon in the genomic DNA. These primers are then used for PCR screening of somatic cell hybrids containing individual human chromosomes. Only those hybrids containing the human gene corresponding to the SEQ ID NO:X will yield an amplified fragment.

20

Similarly, somatic hybrids provide a rapid method of PCR mapping the polynucleotides to particular chromosomes. Three or more clones can be assigned per day using a single thermal cycler. Moreover, sublocalization of the polynucleotides can be achieved with panels of specific chromosome fragments. Other gene mapping strategies that can be used include in situ hybridization, prescreening with labeled flow-sorted chromosomes, and preselection by hybridization to construct chromosome specific-cDNA libraries.

25

Precise chromosomal location of the polynucleotides can also be achieved using fluorescence in situ hybridization (FISH) of a metaphase chromosomal spread. This technique uses polynucleotides as short as 500 or 600 bases; however, polynucleotides 2,000-4,000 bp are preferred. For a review of this technique, see Verma et al., "Human Chromosomes: a Manual of Basic Techniques," Pergamon Press, New York (1988).

30

35

For chromosome mapping, the polynucleotides can be used individually (to mark a single chromosome or a single site on that chromosome) or in panels (for marking multiple sites and/or multiple chromosomes). Preferred polynucleotides correspond to the noncoding regions of the cDNAs because the coding sequences are

more likely conserved within gene families, thus increasing the chance of cross hybridization during chromosomal mapping.

Once a polynucleotide has been mapped to a precise chromosomal location, the physical position of the polynucleotide can be used in linkage analysis. Linkage analysis establishes coinheritance between a chromosomal location and presentation of a particular disease. (Disease mapping data are found, for example, in V. McKusick, Mendelian Inheritance in Man (available on line through Johns Hopkins University Welch Medical Library) .) Assuming 1 megabase mapping resolution and one gene per 20 kb, a cDNA precisely localized to a chromosomal region associated with the disease could be one of 50-500 potential causative genes.

Thus, once coinheritance is established, differences in the polynucleotide and the corresponding gene between affected and unaffected individuals can be examined. First, visible structural alterations in the chromosomes, such as deletions or translocations, are examined in chromosome spreads or by PCR. If no structural alterations exist, the presence of point mutations are ascertained. Mutations observed in some or all affected individuals, but not in normal individuals, indicates that the mutation may cause the disease. However, complete sequencing of the polypeptide and the corresponding gene from several normal individuals is required to distinguish the mutation from a polymorphism. If a new polymorphism is identified, this polymorphic polypeptide can be used for further linkage analysis.

Furthermore, increased or decreased expression of the gene in affected individuals as compared to unaffected individuals can be assessed using polynucleotides of the present invention. Any of these alterations (altered expression, chromosomal rearrangement, or mutation) can be used as a diagnostic or prognostic marker.

In addition to the foregoing, a polynucleotide can be used to control gene expression through triple helix formation or antisense DNA or RNA. Both methods rely on binding of the polynucleotide to DNA or RNA. For these techniques, preferred polynucleotides are usually 20 to 40 bases in length and complementary to either the region of the gene involved in transcription (triple helix - see Lee et al., Nucl. Acids Res. 6:3073 (1979); Cooney et al., Science 241:456 (1988); and Dervan et al., Science 251:1360 (1991) ) or to the mRNA itself (antisense - Okano, J. Neurochem. 56:560 (1991); Oligodeoxy-nucleotides as Antisense Inhibitors of Gene Expression, CRC Press, Boca Raton, FL (1988).) Triple helix formation optimally results in a shut-off of RNA transcription from DNA, while antisense RNA hybridization blocks translation of an mRNA molecule into polypeptide. Both techniques are effective in model

systems, and the information disclosed herein can be used to design antisense or triple helix polynucleotides in an effort to treat disease.

Polynucleotides of the present invention are also useful in gene therapy. One goal of gene therapy is to insert a normal gene into an organism having a defective gene, in an effort to correct the genetic defect. The polynucleotides disclosed in the present invention offer a means of targeting such genetic defects in a highly accurate manner. Another goal is to insert a new gene that was not present in the host genome, thereby producing a new trait in the host cell.

The polynucleotides are also useful for identifying individuals from minute biological samples. The United States military, for example, is considering the use of restriction fragment length polymorphism (RFLP) for identification of its personnel. In this technique, an individual's genomic DNA is digested with one or more restriction enzymes, and probed on a Southern blot to yield unique bands for identifying personnel. This method does not suffer from the current limitations of "Dog Tags" which can be lost, switched, or stolen, making positive identification difficult. The polynucleotides of the present invention can be used as additional DNA markers for RFLP.

The polynucleotides of the present invention can also be used as an alternative to RFLP, by determining the actual base-by-base DNA sequence of selected portions of an individual's genome. These sequences can be used to prepare PCR primers for amplifying and isolating such selected DNA, which can then be sequenced. Using this technique, individuals can be identified because each individual will have a unique set of DNA sequences. Once an unique ID database is established for an individual, positive identification of that individual, living or dead, can be made from extremely small tissue samples.

Forensic biology also benefits from using DNA-based identification techniques as disclosed herein. DNA sequences taken from very small biological samples such as tissues, e.g., hair or skin, or body fluids, e.g., blood, saliva, semen, etc., can be amplified using PCR. In one prior art technique, gene sequences amplified from polymorphic loci, such as DQa class II HLA gene, are used in forensic biology to identify individuals. (Erlich, H., PCR Technology, Freeman and Co. (1992).) Once these specific polymorphic loci are amplified, they are digested with one or more restriction enzymes, yielding an identifying set of bands on a Southern blot probed with DNA corresponding to the DQa class II HLA gene. Similarly, polynucleotides of the present invention can be used as polymorphic markers for forensic purposes.

There is also a need for reagents capable of identifying the source of a particular tissue. Such need arises, for example, in forensics when presented with tissue of

unknown origin. Appropriate reagents can comprise, for example, DNA probes or primers specific to particular tissue prepared from the sequences of the present invention. Panels of such reagents can identify tissue by species and/or by organ type. In a similar fashion, these reagents can be used to screen tissue cultures for contamination.

In the very least, the polynucleotides of the present invention can be used as molecular weight markers on Southern gels, as diagnostic probes for the presence of a specific mRNA in a particular cell type, as a probe to "subtract-out" known sequences in the process of discovering novel polynucleotides, for selecting and making oligomers for attachment to a "gene chip" or other support, to raise anti-DNA antibodies using DNA immunization techniques, and as an antigen to elicit an immune response.

### Uses of the Polypeptides

Each of the polypeptides identified herein can be used in numerous ways. The following description should be considered exemplary and utilizes known techniques.

A polypeptide of the present invention can be used to assay protein levels in a biological sample using antibody-based techniques. For example, protein expression in tissues can be studied with classical immunohistological methods. (Jalkanen, M., et al., J. Cell. Biol. 101:976-985 (1985); Jalkanen, M., et al., J. Cell. Biol. 105:3087-3096 (1987).) Other antibody-based methods useful for detecting protein gene expression include immunoassays, such as the enzyme linked immunosorbent assay (ELISA) and the radioimmunoassay (RIA). Suitable antibody assay labels are known in the art and include enzyme labels, such as, glucose oxidase, and radioisotopes, such as iodine ( $^{125}\text{I}$ ,  $^{121}\text{I}$ ), carbon ( $^{14}\text{C}$ ), sulfur ( $^{35}\text{S}$ ), tritium ( $^3\text{H}$ ), indium ( $^{112}\text{In}$ ), and technetium ( $^{99\text{m}}\text{Tc}$ ), and fluorescent labels, such as fluorescein and rhodamine, and biotin.

In addition to assaying secreted protein levels in a biological sample, proteins can also be detected in vivo by imaging. Antibody labels or markers for in vivo imaging of protein include those detectable by X-radiography, NMR or ESR. For X-radiography, suitable labels include radioisotopes such as barium or cesium, which emit detectable radiation but are not overtly harmful to the subject. Suitable markers for NMR and ESR include those with a detectable characteristic spin, such as deuterium, which may be incorporated into the antibody by labeling of nutrients for the relevant hybridoma.

A protein-specific antibody or antibody fragment which has been labeled with an appropriate detectable imaging moiety, such as a radioisotope (for example,  $^{131}\text{I}$ ,  $^{112}\text{In}$ ,  $^{99\text{m}}\text{Tc}$ ), a radio-opaque substance, or a material detectable by nuclear magnetic

resonance, is introduced (for example, parenterally, subcutaneously, or intraperitoneally) into the mammal. It will be understood in the art that the size of the subject and the imaging system used will determine the quantity of imaging moiety needed to produce diagnostic images. In the case of a radioisotope moiety, for a human  
5 subject, the quantity of radioactivity injected will normally range from about 5 to 20 millicuries of <sup>99m</sup>Tc. The labeled antibody or antibody fragment will then preferentially accumulate at the location of cells which contain the specific protein. In vivo tumor imaging is described in S.W. Burchiel et al., "Immunopharmacokinetics of Radiolabeled Antibodies and Their Fragments." (Chapter 13 in Tumor Imaging: The  
10 Radiochemical Detection of Cancer, S.W. Burchiel and B. A. Rhodes, eds., Masson Publishing Inc. (1982).)

Thus, the invention provides a diagnostic method of a disorder, which involves (a) assaying the expression of a polypeptide of the present invention in cells or body fluid of an individual; (b) comparing the level of gene expression with a standard gene  
15 expression level, whereby an increase or decrease in the assayed polypeptide gene expression level compared to the standard expression level is indicative of a disorder.

Moreover, polypeptides of the present invention can be used to treat disease. For example, patients can be administered a polypeptide of the present invention in an effort to replace absent or decreased levels of the polypeptide (e.g., insulin), to  
20 supplement absent or decreased levels of a different polypeptide (e.g., hemoglobin S for hemoglobin B), to inhibit the activity of a polypeptide (e.g., an oncogene), to activate the activity of a polypeptide (e.g., by binding to a receptor), to reduce the activity of a membrane bound receptor by competing with it for free ligand (e.g., soluble TNF receptors used in reducing inflammation), or to bring about a desired  
25 response (e.g., blood vessel growth).

Similarly, antibodies directed to a polypeptide of the present invention can also be used to treat disease. For example, administration of an antibody directed to a polypeptide of the present invention can bind and reduce overproduction of the polypeptide. Similarly, administration of an antibody can activate the polypeptide, such  
30 as by binding to a polypeptide bound to a membrane (receptor).

At the very least, the polypeptides of the present invention can be used as molecular weight markers on SDS-PAGE gels or on molecular sieve gel filtration columns using methods well known to those of skill in the art. Polypeptides can also be used to raise antibodies, which in turn are used to measure protein expression from a  
35 recombinant cell, as a way of assessing transformation of the host cell. Moreover, the polypeptides of the present invention can be used to test the following biological activities.

### **Biological Activities**

The polynucleotides and polypeptides of the present invention can be used in assays to test for one or more biological activities. If these polynucleotides and polypeptides do exhibit activity in a particular assay, it is likely that these molecules may be involved in the diseases associated with the biological activity. Thus, the polynucleotides and polypeptides could be used to treat the associated disease.

### **Immune Activity**

A polypeptide or polynucleotide of the present invention may be useful in treating deficiencies or disorders of the immune system, by activating or inhibiting the proliferation, differentiation, or mobilization (chemotaxis) of immune cells. Immune cells develop through a process called hematopoiesis, producing myeloid (platelets, red blood cells, neutrophils, and macrophages) and lymphoid (B and T lymphocytes) cells from pluripotent stem cells. The etiology of these immune deficiencies or disorders may be genetic, somatic, such as cancer or some autoimmune disorders, acquired (e.g., by chemotherapy or toxins), or infectious. Moreover, a polynucleotide or polypeptide of the present invention can be used as a marker or detector of a particular immune system disease or disorder.

A polynucleotide or polypeptide of the present invention may be useful in treating or detecting deficiencies or disorders of hematopoietic cells. A polypeptide or polynucleotide of the present invention could be used to increase differentiation and proliferation of hematopoietic cells, including the pluripotent stem cells, in an effort to treat those disorders associated with a decrease in certain (or many) types hematopoietic cells. Examples of immunologic deficiency syndromes include, but are not limited to: blood protein disorders (e.g. agammaglobulinemia, dysgammaglobulinemia), ataxia telangiectasia, common variable immunodeficiency, Digeorge Syndrome, HIV infection, HTLV-BLV infection, leukocyte adhesion deficiency syndrome, lymphopenia, phagocyte bactericidal dysfunction, severe combined immunodeficiency (SCIDs), Wiskott-Aldrich Disorder, anemia, thrombocytopenia, or hemoglobinuria.

Moreover, a polypeptide or polynucleotide of the present invention could also be used to modulate hemostatic (the stopping of bleeding) or thrombolytic activity (clot formation). For example, by increasing hemostatic or thrombolytic activity, a polynucleotide or polypeptide of the present invention could be used to treat blood coagulation disorders (e.g., afibrinogenemia, factor deficiencies), blood platelet disorders (e.g. thrombocytopenia), or wounds resulting from trauma, surgery, or other causes. Alternatively, a polynucleotide or polypeptide of the present invention that can

decrease hemostatic or thrombolytic activity could be used to inhibit or dissolve clotting. These molecules could be important in the treatment of heart attacks (infarction), strokes, or scarring.

5 A polynucleotide or polypeptide of the present invention may also be useful in treating or detecting autoimmune disorders. Many autoimmune disorders result from inappropriate recognition of self as foreign material by immune cells. This inappropriate recognition results in an immune response leading to the destruction of the host tissue. Therefore, the administration of a polypeptide or polynucleotide of the present invention that inhibits an immune response, particularly the proliferation, 10 differentiation, or chemotaxis of T-cells, may be an effective therapy in preventing autoimmune disorders.

Examples of autoimmune disorders that can be treated or detected by the present invention include, but are not limited to: Addison's Disease, hemolytic anemia, antiphospholipid syndrome, rheumatoid arthritis, dermatitis, allergic encephalomyelitis, 15 glomerulonephritis, Goodpasture's Syndrome, Graves' Disease, Multiple Sclerosis, Myasthenia Gravis, Neuritis, Ophthalmia, Bullous Pemphigoid, Pemphigus, Polyendocrinopathies, Purpura, Reiter's Disease, Stiff-Man Syndrome, Autoimmune Thyroiditis, Systemic Lupus Erythematosus, Autoimmune Pulmonary Inflammation, Guillain-Barre Syndrome, insulin dependent diabetes mellitus, and autoimmune 20 inflammatory eye disease.

Similarly, allergic reactions and conditions, such as asthma (particularly allergic asthma) or other respiratory problems, may also be treated by a polypeptide or polynucleotide of the present invention. Moreover, these molecules can be used to treat anaphylaxis, hypersensitivity to an antigenic molecule, or blood group incompatibility.

25 A polynucleotide or polypeptide of the present invention may also be used to treat and/or prevent organ rejection or graft-versus-host disease (GVHD). Organ rejection occurs by host immune cell destruction of the transplanted tissue through an immune response. Similarly, an immune response is also involved in GVHD, but, in this case, the foreign transplanted immune cells destroy the host tissues. The 30 administration of a polypeptide or polynucleotide of the present invention that inhibits an immune response, particularly the proliferation, differentiation, or chemotaxis of T-cells, may be an effective therapy in preventing organ rejection or GVHD.

Similarly, a polypeptide or polynucleotide of the present invention may also be used to modulate inflammation. For example, the polypeptide or polynucleotide may 35 inhibit the proliferation and differentiation of cells involved in an inflammatory response. These molecules can be used to treat inflammatory conditions, both chronic and acute conditions, including inflammation associated with infection (e.g., septic



shock, sepsis, or systemic inflammatory response syndrome (SIRS)), ischemia-reperfusion injury, endotoxin lethality, arthritis, complement-mediated hyperacute rejection, nephritis, cytokine or chemokine induced lung injury, inflammatory bowel disease, Crohn's disease, or resulting from over production of cytokines (e.g., TNF or IL-1.)

### **Hyperproliferative Disorders**

A polypeptide or polynucleotide can be used to treat or detect hyperproliferative disorders, including neoplasms. A polypeptide or polynucleotide of the present invention may inhibit the proliferation of the disorder through direct or indirect interactions. Alternatively, a polypeptide or polynucleotide of the present invention may proliferate other cells which can inhibit the hyperproliferative disorder.

For example, by increasing an immune response, particularly increasing antigenic qualities of the hyperproliferative disorder or by proliferating, differentiating, or mobilizing T-cells, hyperproliferative disorders can be treated. This immune response may be increased by either enhancing an existing immune response, or by initiating a new immune response. Alternatively, decreasing an immune response may also be a method of treating hyperproliferative disorders, such as a chemotherapeutic agent.

Examples of hyperproliferative disorders that can be treated or detected by a polynucleotide or polypeptide of the present invention include, but are not limited to neoplasms located in the: abdomen, bone, breast, digestive system, liver, pancreas, peritoneum, endocrine glands (adrenal, parathyroid, pituitary, testicles, ovary, thymus, thyroid), eye, head and neck, nervous (central and peripheral), lymphatic system, pelvic, skin, soft tissue, spleen, thoracic, and urogenital.

Similarly, other hyperproliferative disorders can also be treated or detected by a polynucleotide or polypeptide of the present invention. Examples of such hyperproliferative disorders include, but are not limited to: hypergammaglobulinemia, lymphoproliferative disorders, paraproteinemias, purpura, sarcoidosis, Sezary Syndrome, Waldenstrom's Macroglobulinemia, Gaucher's Disease, histiocytosis, and any other hyperproliferative disease, besides neoplasia, located in an organ system listed above.

### **Infectious Disease**

A polypeptide or polynucleotide of the present invention can be used to treat or detect infectious agents. For example, by increasing the immune response, particularly increasing the proliferation and differentiation of B and/or T cells, infectious diseases

may be treated. The immune response may be increased by either enhancing an existing immune response, or by initiating a new immune response. Alternatively, the polypeptide or polynucleotide of the present invention may also directly inhibit the infectious agent, without necessarily eliciting an immune response.

5           Viruses are one example of an infectious agent that can cause disease or symptoms that can be treated or detected by a polynucleotide or polypeptide of the present invention. Examples of viruses, include, but are not limited to the following DNA and RNA viral families: Arbovirus, Adenoviridae, Arenaviridae, Arterivirus, Birnaviridae, Bunyaviridae, Caliciviridae, Circoviridae, Coronaviridae, Flaviviridae, 10 Hepadnaviridae (Hepatitis), Herpesviridae (such as, Cytomegalovirus, Herpes Simplex, Herpes Zoster), Mononegavirus (e.g., Paramyxoviridae, Morbillivirus, Rhabdoviridae), Orthomyxoviridae (e.g., Influenza), Papovaviridae, Parvoviridae, Picornaviridae, Poxviridae (such as Smallpox or Vaccinia), Reoviridae (e.g., Rotavirus), Retroviridae (HTLV-I, HTLV-II, Lentivirus), and Togaviridae (e.g., 15 Rubivirus). Viruses falling within these families can cause a variety of diseases or symptoms, including, but not limited to: arthritis, bronchiollitis, encephalitis, eye infections (e.g., conjunctivitis, keratitis), chronic fatigue syndrome, hepatitis (A, B, C, E, Chronic Active, Delta), meningitis, opportunistic infections (e.g., AIDS), pneumonia, Burkitt's Lymphoma, chickenpox, hemorrhagic fever, Measles, Mumps, 20 Parainfluenza, Rabies, the common cold, Polio, leukemia, Rubella, sexually transmitted diseases, skin diseases (e.g., Kaposi's, warts), and viremia. A polypeptide or polynucleotide of the present invention can be used to treat or detect any of these symptoms or diseases.

          Similarly, bacterial or fungal agents that can cause disease or symptoms and that 25 can be treated or detected by a polynucleotide or polypeptide of the present invention include, but not limited to, the following Gram-Negative and Gram-positive bacterial families and fungi: Actinomycetales (e.g., Corynebacterium, Mycobacterium, Norcardia), Aspergillosis, Bacillaceae (e.g., Anthrax, Clostridium), Bacteroidaceae, Blastomycosis, Bordetella, Borrelia, Brucellosis, Candidiasis, Campylobacter, 30 Coccidioidomycosis, Cryptococcosis, Dermatocycoses, Enterobacteriaceae (Klebsiella, Salmonella, Serratia, Yersinia), Erysipelothrix, Helicobacter, Legionellosis, Leptospirosis, Listeria, Mycoplasmatales, Neisseriaceae (e.g., Acinetobacter, Gonorrhea, Meningococcal), Pasteurellaceae Infections (e.g., Actinobacillus, Heamophilus, Pasteurella), Pseudomonas, Rickettsiaceae, Chlamydiaceae, Syphilis, 35 and Staphylococcal. These bacterial or fungal families can cause the following diseases or symptoms, including, but not limited to: bacteremia, endocarditis, eye infections (conjunctivitis, tuberculosis, uveitis), gingivitis, opportunistic infections (e.g., AIDS

related infections), paronychia, prosthesis-related infections, Reiter's Disease, respiratory tract infections, such as Whooping Cough or Empyema, sepsis, Lyme Disease, Cat-Scratch Disease, Dysentery, Paratyphoid Fever, food poisoning, Typhoid, pneumonia, Gonorrhea, meningitis, Chlamydia, Syphilis, Diphtheria, Leprosy, Paratuberculosis, Tuberculosis, Lupus, Botulism, gangrene, tetanus, impetigo, Rheumatic Fever, Scarlet Fever, sexually transmitted diseases, skin diseases (e.g., cellulitis, dermatocycoses), toxemia, urinary tract infections, wound infections. A polypeptide or polynucleotide of the present invention can be used to treat or detect any of these symptoms or diseases.

Moreover, parasitic agents causing disease or symptoms that can be treated or detected by a polynucleotide or polypeptide of the present invention include, but not limited to, the following families: Amebiasis, Babesiosis, Coccidiosis, Cryptosporidiosis, Dientamoebiasis, Dourine, Ectoparasitic, Giardiasis, Helminthiasis, Leishmaniasis, Theileriasis, Toxoplasmosis, Trypanosomiasis, and Trichomonas. These parasites can cause a variety of diseases or symptoms, including, but not limited to: Scabies, Trombiculiasis, eye infections, intestinal disease (e.g., dysentery, giardiasis), liver disease, lung disease, opportunistic infections (e.g., AIDS related), Malaria, pregnancy complications, and toxoplasmosis. A polypeptide or polynucleotide of the present invention can be used to treat or detect any of these symptoms or diseases.

Preferably, treatment using a polypeptide or polynucleotide of the present invention could either be by administering an effective amount of a polypeptide to the patient, or by removing cells from the patient, supplying the cells with a polynucleotide of the present invention, and returning the engineered cells to the patient (ex vivo therapy). Moreover, the polypeptide or polynucleotide of the present invention can be used as an antigen in a vaccine to raise an immune response against infectious disease.

### **Regeneration**

A polynucleotide or polypeptide of the present invention can be used to differentiate, proliferate, and attract cells, leading to the regeneration of tissues. (See, Science 276:59-87 (1997).) The regeneration of tissues could be used to repair, replace, or protect tissue damaged by congenital defects, trauma (wounds, burns, incisions, or ulcers), age, disease (e.g. osteoporosis, osteoarthritis, periodontal disease, liver failure), surgery, including cosmetic plastic surgery, fibrosis, reperfusion injury, or systemic cytokine damage.

Tissues that could be regenerated using the present invention include organs (e.g., pancreas, liver, intestine, kidney, skin, endothelium), muscle (smooth, skeletal

or cardiac), vascular (including vascular endothelium), nervous, hematopoietic, and skeletal (bone, cartilage, tendon, and ligament) tissue. Preferably, regeneration occurs without or decreased scarring. Regeneration also may include angiogenesis.

Moreover, a polynucleotide or polypeptide of the present invention may increase  
5 regeneration of tissues difficult to heal. For example, increased tendon/ligament regeneration would quicken recovery time after damage. A polynucleotide or polypeptide of the present invention could also be used prophylactically in an effort to avoid damage. Specific diseases that could be treated include of tendinitis, carpal tunnel syndrome, and other tendon or ligament defects. A further example of tissue  
10 regeneration of non-healing wounds includes pressure ulcers, ulcers associated with vascular insufficiency, surgical, and traumatic wounds.

Similarly, nerve and brain tissue could also be regenerated by using a polynucleotide or polypeptide of the present invention to proliferate and differentiate nerve cells. Diseases that could be treated using this method include central and  
15 peripheral nervous system diseases, neuropathies, or mechanical and traumatic disorders (e.g., spinal cord disorders, head trauma, cerebrovascular disease, and stroke). Specifically, diseases associated with peripheral nerve injuries, peripheral neuropathy (e.g., resulting from chemotherapy or other medical therapies), localized neuropathies, and central nervous system diseases (e.g., Alzheimer's disease,  
20 Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, and Shy-Drager syndrome), could all be treated using the polynucleotide or polypeptide of the present invention.

### Chemotaxis

25 A polynucleotide or polypeptide of the present invention may have chemotaxis activity. A chemotactic molecule attracts or mobilizes cells (e.g., monocytes, fibroblasts, neutrophils, T-cells, mast cells, eosinophils, epithelial and/or endothelial cells) to a particular site in the body, such as inflammation, infection, or site of hyperproliferation. The mobilized cells can then fight off and/or heal the particular  
30 trauma or abnormality.

A polynucleotide or polypeptide of the present invention may increase chemotactic activity of particular cells. These chemotactic molecules can then be used to treat inflammation, infection, hyperproliferative disorders, or any immune system disorder by increasing the number of cells targeted to a particular location in the body.  
35 For example, chemotactic molecules can be used to treat wounds and other trauma to tissues by attracting immune cells to the injured location. Chemotactic molecules of the present invention can also attract fibroblasts, which can be used to treat wounds.

It is also contemplated that a polynucleotide or polypeptide of the present invention may inhibit chemotactic activity. These molecules could also be used to treat disorders. Thus, a polynucleotide or polypeptide of the present invention could be used as an inhibitor of chemotaxis.

5

### **Binding Activity**

A polypeptide of the present invention may be used to screen for molecules that bind to the polypeptide or for molecules to which the polypeptide binds. The binding of the polypeptide and the molecule may activate (agonist), increase, inhibit  
10 (antagonist), or decrease activity of the polypeptide or the molecule bound. Examples of such molecules include antibodies, oligonucleotides, proteins (e.g., receptors), or small molecules.

Preferably, the molecule is closely related to the natural ligand of the polypeptide, e.g., a fragment of the ligand, or a natural substrate, a ligand, a structural  
15 or functional mimetic. (See, Coligan et al., Current Protocols in Immunology 1(2):Chapter 5 (1991).) Similarly, the molecule can be closely related to the natural receptor to which the polypeptide binds, or at least, a fragment of the receptor capable of being bound by the polypeptide (e.g., active site). In either case, the molecule can be rationally designed using known techniques.

20 Preferably, the screening for these molecules involves producing appropriate cells which express the polypeptide, either as a secreted protein or on the cell membrane. Preferred cells include cells from mammals, yeast, *Drosophila*, or *E. coli*. Cells expressing the polypeptide (or cell membrane containing the expressed polypeptide) are then preferably contacted with a test compound potentially containing  
25 the molecule to observe binding, stimulation, or inhibition of activity of either the polypeptide or the molecule.

The assay may simply test binding of a candidate compound to the polypeptide, wherein binding is detected by a label, or in an assay involving competition with a labeled competitor. Further, the assay may test whether the candidate compound results  
30 in a signal generated by binding to the polypeptide.

Alternatively, the assay can be carried out using cell-free preparations, polypeptide/molecule affixed to a solid support, chemical libraries, or natural product mixtures. The assay may also simply comprise the steps of mixing a candidate compound with a solution containing a polypeptide, measuring polypeptide/molecule  
35 activity or binding, and comparing the polypeptide/molecule activity or binding to a standard.

Preferably, an ELISA assay can measure polypeptide level or activity in a sample (e.g., biological sample) using a monoclonal or polyclonal antibody. The antibody can measure polypeptide level or activity by either binding, directly or indirectly, to the polypeptide or by competing with the polypeptide for a substrate.

5 All of these above assays can be used as diagnostic or prognostic markers. The molecules discovered using these assays can be used to treat disease or to bring about a particular result in a patient (e.g., blood vessel growth) by activating or inhibiting the polypeptide/molecule. Moreover, the assays can discover agents which may inhibit or enhance the production of the polypeptide from suitably manipulated cells or tissues.

10 Therefore, the invention includes a method of identifying compounds which bind to a polypeptide of the invention comprising the steps of: (a) incubating a candidate binding compound with a polypeptide of the invention; and (b) determining if binding has occurred. Moreover, the invention includes a method of identifying agonists/antagonists comprising the steps of: (a) incubating a candidate compound with  
15 a polypeptide of the invention, (b) assaying a biological activity, and (b) determining if a biological activity of the polypeptide has been altered.

### Other Activities

A polypeptide or polynucleotide of the present invention may also increase or  
20 decrease the differentiation or proliferation of embryonic stem cells, besides, as discussed above, hematopoietic lineage.

A polypeptide or polynucleotide of the present invention may also be used to modulate mammalian characteristics, such as body height, weight, hair color, eye color, skin, percentage of adipose tissue, pigmentation, size, and shape (e.g., cosmetic  
25 surgery). Similarly, a polypeptide or polynucleotide of the present invention may be used to modulate mammalian metabolism affecting catabolism, anabolism, processing, utilization, and storage of energy.

A polypeptide or polynucleotide of the present invention may be used to change a mammal's mental state or physical state by influencing biorhythms, circadian  
30 rhythms, depression (including depressive disorders), tendency for violence, tolerance for pain, reproductive capabilities (preferably by Activin or Inhibin-like activity), hormonal or endocrine levels, appetite, libido, memory, stress, or other cognitive qualities.

A polypeptide or polynucleotide of the present invention may also be used as a  
35 food additive or preservative, such as to increase or decrease storage capabilities, fat content, lipid, protein, carbohydrate, vitamins, minerals, cofactors or other nutritional components.

### **Other Preferred Embodiments**

Other preferred embodiments of the claimed invention include an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to a sequence of at least about 50 contiguous nucleotides in the nucleotide sequence of SEQ ID NO:X wherein X is any integer as defined in Table 1.

Also preferred is a nucleic acid molecule wherein said sequence of contiguous nucleotides is included in the nucleotide sequence of SEQ ID NO:X in the range of positions beginning with the nucleotide at about the position of the 5' Nucleotide of the Clone Sequence and ending with the nucleotide at about the position of the 3' Nucleotide of the Clone Sequence as defined for SEQ ID NO:X in Table 1.

Also preferred is a nucleic acid molecule wherein said sequence of contiguous nucleotides is included in the nucleotide sequence of SEQ ID NO:X in the range of positions beginning with the nucleotide at about the position of the 5' Nucleotide of the Start Codon and ending with the nucleotide at about the position of the 3' Nucleotide of the Clone Sequence as defined for SEQ ID NO:X in Table 1.

Similarly preferred is a nucleic acid molecule wherein said sequence of contiguous nucleotides is included in the nucleotide sequence of SEQ ID NO:X in the range of positions beginning with the nucleotide at about the position of the 5' Nucleotide of the First Amino Acid of the Signal Peptide and ending with the nucleotide at about the position of the 3' Nucleotide of the Clone Sequence as defined for SEQ ID NO:X in Table 1.

Also preferred is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to a sequence of at least about 150 contiguous nucleotides in the nucleotide sequence of SEQ ID NO:X.

Further preferred is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to a sequence of at least about 500 contiguous nucleotides in the nucleotide sequence of SEQ ID NO:X.

A further preferred embodiment is a nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to the nucleotide sequence of SEQ ID NO:X beginning with the nucleotide at about the position of the 5' Nucleotide of the First Amino Acid of the Signal Peptide and ending with the nucleotide at about the position of the 3' Nucleotide of the Clone Sequence as defined for SEQ ID NO:X in Table 1.

A further preferred embodiment is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to the complete nucleotide sequence of SEQ ID NO:X.

Also preferred is an isolated nucleic acid molecule which hybridizes under stringent hybridization conditions to a nucleic acid molecule, wherein said nucleic acid molecule which hybridizes does not hybridize under stringent hybridization conditions to a nucleic acid molecule having a nucleotide sequence consisting of only A residues or of only T residues.

Also preferred is a composition of matter comprising a DNA molecule which comprises a human cDNA clone identified by a cDNA Clone Identifier in Table 1, which DNA molecule is contained in the material deposited with the American Type Culture Collection and given the ATCC Deposit Number shown in Table 1 for said cDNA Clone Identifier.

Also preferred is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to a sequence of at least 50 contiguous nucleotides in the nucleotide sequence of a human cDNA clone identified by a cDNA Clone Identifier in Table 1, which DNA molecule is contained in the deposit given the ATCC Deposit Number shown in Table 1.

Also preferred is an isolated nucleic acid molecule, wherein said sequence of at least 50 contiguous nucleotides is included in the nucleotide sequence of the complete open reading frame sequence encoded by said human cDNA clone.

Also preferred is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to sequence of at least 150 contiguous nucleotides in the nucleotide sequence encoded by said human cDNA clone.

A further preferred embodiment is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to sequence of at least 500 contiguous nucleotides in the nucleotide sequence encoded by said human cDNA clone.

A further preferred embodiment is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to the complete nucleotide sequence encoded by said human cDNA clone.

A further preferred embodiment is a method for detecting in a biological sample a nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to a sequence of at least 50 contiguous nucleotides in a sequence selected from the group consisting of: a nucleotide sequence of SEQ ID NO:X wherein X is any integer as defined in Table 1; and a nucleotide sequence encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1; which method



comprises a step of comparing a nucleotide sequence of at least one nucleic acid molecule in said sample with a sequence selected from said group and determining whether the sequence of said nucleic acid molecule in said sample is at least 95% identical to said selected sequence.

5 Also preferred is the above method wherein said step of comparing sequences comprises determining the extent of nucleic acid hybridization between nucleic acid molecules in said sample and a nucleic acid molecule comprising said sequence selected from said group. Similarly, also preferred is the above method wherein said step of  
10 comparing sequences is performed by comparing the nucleotide sequence determined from a nucleic acid molecule in said sample with said sequence selected from said group. The nucleic acid molecules can comprise DNA molecules or RNA molecules.

A further preferred embodiment is a method for identifying the species, tissue or cell type of a biological sample which method comprises a step of detecting nucleic acid molecules in said sample, if any, comprising a nucleotide sequence that is at least 95%  
15 identical to a sequence of at least 50 contiguous nucleotides in a sequence selected from the group consisting of: a nucleotide sequence of SEQ ID NO:X wherein X is any integer as defined in Table 1; and a nucleotide sequence encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

20 The method for identifying the species, tissue or cell type of a biological sample can comprise a step of detecting nucleic acid molecules comprising a nucleotide sequence in a panel of at least two nucleotide sequences, wherein at least one sequence in said panel is at least 95% identical to a sequence of at least 50 contiguous nucleotides in a sequence selected from said group.

25 Also preferred is a method for diagnosing in a subject a pathological condition associated with abnormal structure or expression of a gene encoding a secreted protein identified in Table 1, which method comprises a step of detecting in a biological sample obtained from said subject nucleic acid molecules, if any, comprising a nucleotide sequence that is at least 95% identical to a sequence of at least 50 contiguous  
30 nucleotides in a sequence selected from the group consisting of: a nucleotide sequence of SEQ ID NO:X wherein X is any integer as defined in Table 1; and a nucleotide sequence encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

35 The method for diagnosing a pathological condition can comprise a step of detecting nucleic acid molecules comprising a nucleotide sequence in a panel of at least two nucleotide sequences, wherein at least one sequence in said panel is at least 95%

identical to a sequence of at least 50 contiguous nucleotides in a sequence selected from said group.

Also preferred is a composition of matter comprising isolated nucleic acid molecules wherein the nucleotide sequences of said nucleic acid molecules comprise a panel of at least two nucleotide sequences, wherein at least one sequence in said panel is at least 95% identical to a sequence of at least 50 contiguous nucleotides in a sequence selected from the group consisting of: a nucleotide sequence of SEQ ID NO:X wherein X is any integer as defined in Table 1; and a nucleotide sequence encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1. The nucleic acid molecules can comprise DNA molecules or RNA molecules.

Also preferred is an isolated polypeptide comprising an amino acid sequence at least 90% identical to a sequence of at least about 10 contiguous amino acids in the amino acid sequence of SEQ ID NO:Y wherein Y is any integer as defined in Table 1.

Also preferred is a polypeptide, wherein said sequence of contiguous amino acids is included in the amino acid sequence of SEQ ID NO:Y in the range of positions beginning with the residue at about the position of the First Amino Acid of the Secreted Portion and ending with the residue at about the Last Amino Acid of the Open Reading Frame as set forth for SEQ ID NO:Y in Table 1.

Also preferred is an isolated polypeptide comprising an amino acid sequence at least 95% identical to a sequence of at least about 30 contiguous amino acids in the amino acid sequence of SEQ ID NO:Y.

Further preferred is an isolated polypeptide comprising an amino acid sequence at least 95% identical to a sequence of at least about 100 contiguous amino acids in the amino acid sequence of SEQ ID NO:Y.

Further preferred is an isolated polypeptide comprising an amino acid sequence at least 95% identical to the complete amino acid sequence of SEQ ID NO:Y.

Further preferred is an isolated polypeptide comprising an amino acid sequence at least 90% identical to a sequence of at least about 10 contiguous amino acids in the complete amino acid sequence of a secreted protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

Also preferred is a polypeptide wherein said sequence of contiguous amino acids is included in the amino acid sequence of a secreted portion of the secreted protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

Also preferred is an isolated polypeptide comprising an amino acid sequence at least 95% identical to a sequence of at least about 30 contiguous amino acids in the amino acid sequence of the secreted portion of the protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

Also preferred is an isolated polypeptide comprising an amino acid sequence at least 95% identical to a sequence of at least about 100 contiguous amino acids in the amino acid sequence of the secreted portion of the protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

Also preferred is an isolated polypeptide comprising an amino acid sequence at least 95% identical to the amino acid sequence of the secreted portion of the protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

Further preferred is an isolated antibody which binds specifically to a polypeptide comprising an amino acid sequence that is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the group consisting of: an amino acid sequence of SEQ ID NO:Y wherein Y is any integer as defined in Table 1; and a complete amino acid sequence of a protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

Further preferred is a method for detecting in a biological sample a polypeptide comprising an amino acid sequence which is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the group consisting of: an amino acid sequence of SEQ ID NO:Y wherein Y is any integer as defined in Table 1; and a complete amino acid sequence of a protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1; which method comprises a step of comparing an amino acid sequence of at least one polypeptide molecule in said sample with a sequence selected from said group and determining whether the sequence of said polypeptide molecule in said sample is at least 90% identical to said sequence of at least 10 contiguous amino acids.

Also preferred is the above method wherein said step of comparing an amino acid sequence of at least one polypeptide molecule in said sample with a sequence selected from said group comprises determining the extent of specific binding of polypeptides in said sample to an antibody which binds specifically to a polypeptide

comprising an amino acid sequence that is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the group consisting of: an amino acid sequence of SEQ ID NO:Y wherein Y is any integer as defined in Table 1; and a complete amino acid sequence of a protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

Also preferred is the above method wherein said step of comparing sequences is performed by comparing the amino acid sequence determined from a polypeptide molecule in said sample with said sequence selected from said group.

Also preferred is a method for identifying the species, tissue or cell type of a biological sample which method comprises a step of detecting polypeptide molecules in said sample, if any, comprising an amino acid sequence that is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the group consisting of: an amino acid sequence of SEQ ID NO:Y wherein Y is any integer as defined in Table 1; and a complete amino acid sequence of a secreted protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

Also preferred is the above method for identifying the species, tissue or cell type of a biological sample, which method comprises a step of detecting polypeptide molecules comprising an amino acid sequence in a panel of at least two amino acid sequences, wherein at least one sequence in said panel is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the above group.

Also preferred is a method for diagnosing in a subject a pathological condition associated with abnormal structure or expression of a gene encoding a secreted protein identified in Table 1, which method comprises a step of detecting in a biological sample obtained from said subject polypeptide molecules comprising an amino acid sequence in a panel of at least two amino acid sequences, wherein at least one sequence in said panel is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the group consisting of: an amino acid sequence of SEQ ID NO:Y wherein Y is any integer as defined in Table 1; and a complete amino acid sequence of a secreted protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

In any of these methods, the step of detecting said polypeptide molecules includes using an antibody.

Also preferred is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to a nucleotide sequence encoding a polypeptide wherein said polypeptide comprises an amino acid sequence that is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the group consisting of: an amino acid sequence of SEQ ID NO:Y wherein Y is any integer as defined in Table 1; and a complete amino acid sequence of a secreted protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

Also preferred is an isolated nucleic acid molecule, wherein said nucleotide sequence encoding a polypeptide has been optimized for expression of said polypeptide in a prokaryotic host.

Also preferred is an isolated nucleic acid molecule, wherein said polypeptide comprises an amino acid sequence selected from the group consisting of: an amino acid sequence of SEQ ID NO:Y wherein Y is any integer as defined in Table 1; and a complete amino acid sequence of a secreted protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

Further preferred is a method of making a recombinant vector comprising inserting any of the above isolated nucleic acid molecule into a vector. Also preferred is the recombinant vector produced by this method. Also preferred is a method of making a recombinant host cell comprising introducing the vector into a host cell, as well as the recombinant host cell produced by this method.

Also preferred is a method of making an isolated polypeptide comprising culturing this recombinant host cell under conditions such that said polypeptide is expressed and recovering said polypeptide. Also preferred is this method of making an isolated polypeptide, wherein said recombinant host cell is a eukaryotic cell and said polypeptide is a secreted portion of a human secreted protein comprising an amino acid sequence selected from the group consisting of: an amino acid sequence of SEQ ID NO:Y beginning with the residue at the position of the First Amino Acid of the Secreted Portion of SEQ ID NO:Y wherein Y is an integer set forth in Table 1 and said position of the First Amino Acid of the Secreted Portion of SEQ ID NO:Y is defined in Table 1; and an amino acid sequence of a secreted portion of a protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1. The isolated polypeptide produced by this method is also preferred.

Also preferred is a method of treatment of an individual in need of an increased level of a secreted protein activity, which method comprises administering to such an individual a pharmaceutical composition comprising an amount of an isolated polypeptide, polynucleotide, or antibody of the claimed invention effective to increase the level of said protein activity in said individual.

Having generally described the invention, the same will be more readily understood by reference to the following examples, which are provided by way of illustration and are not intended as limiting.

### Examples

#### Example 1: Isolation of a Selected cDNA Clone From the Deposited Sample

Each cDNA clone in a cited ATCC deposit is contained in a plasmid vector. Table 1 identifies the vectors used to construct the cDNA library from which each clone was isolated. In many cases, the vector used to construct the library is a phage vector from which a plasmid has been excised. The table immediately below correlates the related plasmid for each phage vector used in constructing the cDNA library. For example, where a particular clone is identified in Table 1 as being isolated in the vector "Lambda Zap," the corresponding deposited clone is in "pBluescript."

<u>Vector Used to Construct Library</u>	<u>Corresponding Deposited Plasmid</u>
Lambda Zap	pBluescript (pBS)
Uni-Zap XR	pBluescript (pBS)
Zap Express	pBK
lafmid BA	plafmid BA
pSport1	pSport1
pCMVSPORT 2.0	pCMVSPORT 2.0
pCMVSPORT 3.0	pCMVSPORT 3.0
pCR <sup>®</sup> 2.1	pCR <sup>®</sup> 2.1

Vectors Lambda Zap (U.S. Patent Nos. 5,128,256 and 5,286,636), Uni-Zap XR (U.S. Patent Nos. 5,128, 256 and 5,286,636), Zap Express (U.S. Patent Nos. 5,128,256 and 5,286,636), pBluescript (pBS) (Short, J. M. et al., Nucleic Acids Res. 16:7583-7600 (1988); Alting-Mees, M. A. and Short, J. M., Nucleic Acids Res. 17:9494 (1989)) and pBK (Alting-Mees, M. A. et al., Strategies 5:58-61 (1992)) are commercially available from Stratagene Cloning Systems, Inc., 11011 N. Torrey Pines Road, La Jolla, CA, 92037. pBS contains an ampicillin resistance gene and pBK contains a neomycin resistance gene. Both can be transformed into E. coli strain XL-1

Blue, also available from Stratagene. pBS comes in 4 forms SK+, SK-, KS+ and KS-. The S and K refers to the orientation of the polylinker to the T7 and T3 primer sequences which flank the polylinker region ("S" is for SacI and "K" is for KpnI which are the first sites on each respective end of the linker). "+" or "-" refer to the orientation of the fl ori origin of replication ("ori"), such that in one orientation, single stranded rescue initiated from the fl ori generates sense strand DNA and in the other, antisense.

Vectors pSport1, pCMVSPORT 2.0 and pCMVSPORT 3.0, were obtained from Life Technologies, Inc., P. O. Box 6009, Gaithersburg, MD 20897. All Sport vectors contain an ampicillin resistance gene and may be transformed into E. coli strain DH10B, also available from Life Technologies. (See, for instance, Gruber, C. E., et al., Focus 15:59 (1993).) Vector lafmid BA (Bento Soares, Columbia University, NY) contains an ampicillin resistance gene and can be transformed into E. coli strain XL-1 Blue. Vector pCR<sup>®</sup>2.1, which is available from Invitrogen, 1600 Faraday Avenue, Carlsbad, CA 92008, contains an ampicillin resistance gene and may be transformed into E. coli strain DH10B, available from Life Technologies. (See, for instance, Clark, J. M., Nuc. Acids Res. 16:9677-9686 (1988) and Mead, D. et al., Bio/Technology 9: (1991).) Preferably, a polynucleotide of the present invention does not comprise the phage vector sequences identified for the particular clone in Table 1, as well as the corresponding plasmid vector sequences designated above.

The deposited material in the sample assigned the ATCC Deposit Number cited in Table 1 for any given cDNA clone also may contain one or more additional plasmids, each comprising a cDNA clone different from that given clone. Thus, deposits sharing the same ATCC Deposit Number contain at least a plasmid for each cDNA clone identified in Table 1. Typically, each ATCC deposit sample cited in Table 1 comprises a mixture of approximately equal amounts (by weight) of about 50 plasmid DNAs, each containing a different cDNA clone; but such a deposit sample may include plasmids for more or less than 50 cDNA clones, up to about 500 cDNA clones.

Two approaches can be used to isolate a particular clone from the deposited sample of plasmid DNAs cited for that clone in Table 1. First, a plasmid is directly isolated by screening the clones using a polynucleotide probe corresponding to SEQ ID NO:X.

Particularly, a specific polynucleotide with 30-40 nucleotides is synthesized using an Applied Biosystems DNA synthesizer according to the sequence reported. The oligonucleotide is labeled, for instance, with <sup>32</sup>P-γ-ATP using T4 polynucleotide kinase and purified according to routine methods. (E.g., Maniatis et al., Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Press, Cold Spring, NY (1982).)

The plasmid mixture is transformed into a suitable host, as indicated above (such as XL-1 Blue (Stratagene)) using techniques known to those of skill in the art, such as those provided by the vector supplier or in related publications or patents cited above. The transformants are plated on 1.5% agar plates (containing the appropriate selection agent, e.g., ampicillin) to a density of about 150 transformants (colonies) per plate. These plates are screened using Nylon membranes according to routine methods for bacterial colony screening (e.g., Sambrook et al., *Molecular Cloning: A Laboratory Manual*, 2nd Edit., (1989), Cold Spring Harbor Laboratory Press, pages 1.93 to 1.104), or other techniques known to those of skill in the art.

Alternatively, two primers of 17-20 nucleotides derived from both ends of the SEQ ID NO:X (i.e., within the region of SEQ ID NO:X bounded by the 5' NT and the 3' NT of the clone defined in Table 1) are synthesized and used to amplify the desired cDNA using the deposited cDNA plasmid as a template. The polymerase chain reaction is carried out under routine conditions, for instance, in 25  $\mu$ l of reaction mixture with 0.5  $\mu$ g of the above cDNA template. A convenient reaction mixture is 1.5-5 mM  $MgCl_2$ , 0.01% (w/v) gelatin, 20  $\mu$ M each of dATP, dCTP, dGTP, dTTP, 25 pmol of each primer and 0.25 Unit of Taq polymerase. Thirty five cycles of PCR (denaturation at 94°C for 1 min; annealing at 55°C for 1 min; elongation at 72°C for 1 min) are performed with a Perkin-Elmer Cetus automated thermal cycler. The amplified product is analyzed by agarose gel electrophoresis and the DNA band with expected molecular weight is excised and purified. The PCR product is verified to be the selected sequence by subcloning and sequencing the DNA product.

Several methods are available for the identification of the 5' or 3' non-coding portions of a gene which may not be present in the deposited clone. These methods include but are not limited to, filter probing, clone enrichment using specific probes, and protocols similar or identical to 5' and 3' "RACE" protocols which are well known in the art. For instance, a method similar to 5' RACE is available for generating the missing 5' end of a desired full-length transcript. (Fromont-Racine et al., *Nucleic Acids Res.* 21(7):1683-1684 (1993).)

Briefly, a specific RNA oligonucleotide is ligated to the 5' ends of a population of RNA presumably containing full-length gene RNA transcripts. A primer set containing a primer specific to the ligated RNA oligonucleotide and a primer specific to a known sequence of the gene of interest is used to PCR amplify the 5' portion of the desired full-length gene. This amplified product may then be sequenced and used to generate the full length gene.



This above method starts with total RNA isolated from the desired source, although poly-A+ RNA can be used. The RNA preparation can then be treated with phosphatase if necessary to eliminate 5' phosphate groups on degraded or damaged RNA which may interfere with the later RNA ligase step. The phosphatase should then  
5 be inactivated and the RNA treated with tobacco acid pyrophosphatase in order to remove the cap structure present at the 5' ends of messenger RNAs. This reaction leaves a 5' phosphate group at the 5' end of the cap cleaved RNA which can then be ligated to an RNA oligonucleotide using T4 RNA ligase.

This modified RNA preparation is used as a template for first strand cDNA  
10 synthesis using a gene specific oligonucleotide. The first strand synthesis reaction is used as a template for PCR amplification of the desired 5' end using a primer specific to the ligated RNA oligonucleotide and a primer specific to the known sequence of the gene of interest. The resultant product is then sequenced and analyzed to confirm that the 5' end sequence belongs to the desired gene.

#### **Example 2: Isolation of Genomic Clones Corresponding to a Polynucleotide**

A human genomic P1 library (Genomic Systems, Inc.) is screened by PCR  
20 using primers selected for the cDNA sequence corresponding to SEQ ID NO:X., according to the method described in Example 1. (See also, Sambrook.)

#### **Example 3: Tissue Distribution of Polypeptide**

Tissue distribution of mRNA expression of polynucleotides of the present invention is determined using protocols for Northern blot analysis, described by,  
25 among others, Sambrook et al. For example, a cDNA probe produced by the method described in Example 1 is labeled with P<sup>32</sup> using the rediprime™ DNA labeling system (Amersham Life Science), according to manufacturer's instructions. After labeling, the probe is purified using CHROMA SPIN-100™ column (Clontech Laboratories, Inc.), according to manufacturer's protocol number PT1200-1. The purified labeled probe is  
30 then used to examine various human tissues for mRNA expression.

Multiple Tissue Northern (MTN) blots containing various human tissues (H) or human immune system tissues (IM) (Clontech) are examined with the labeled probe using ExpressHyb™ hybridization solution (Clontech) according to manufacturer's protocol number PT1190-1. Following hybridization and washing, the blots are  
35 mounted and exposed to film at -70°C overnight, and the films developed according to standard procedures.

**Example 4: Chromosomal Mapping of the Polynucleotides**

An oligonucleotide primer set is designed according to the sequence at the 5' end of SEQ ID NO:X. This primer preferably spans about 100 nucleotides. This primer set is then used in a polymerase chain reaction under the following set of conditions : 30 seconds, 95°C; 1 minute, 56°C; 1 minute, 70°C. This cycle is repeated 32 times followed by one 5 minute cycle at 70°C. Human, mouse, and hamster DNA is used as template in addition to a somatic cell hybrid panel containing individual chromosomes or chromosome fragments (Bios, Inc). The reactions is analyzed on either 8% polyacrylamide gels or 3.5 % agarose gels. Chromosome mapping is determined by the presence of an approximately 100 bp PCR fragment in the particular somatic cell hybrid.

**Example 5: Bacterial Expression of a Polypeptide**

A polynucleotide encoding a polypeptide of the present invention is amplified using PCR oligonucleotide primers corresponding to the 5' and 3' ends of the DNA sequence, as outlined in Example 1, to synthesize insertion fragments. The primers used to amplify the cDNA insert should preferably contain restriction sites, such as BamHI and XbaI, at the 5' end of the primers in order to clone the amplified product into the expression vector. For example, BamHI and XbaI correspond to the restriction enzyme sites on the bacterial expression vector pQE-9. (Qiagen, Inc., Chatsworth, CA). This plasmid vector encodes antibiotic resistance (Amp<sup>r</sup>), a bacterial origin of replication (ori), an IPTG-regulatable promoter/operator (P/O), a ribosome binding site (RBS), a 6-histidine tag (6-His), and restriction enzyme cloning sites.

The pQE-9 vector is digested with BamHI and XbaI and the amplified fragment is ligated into the pQE-9 vector maintaining the reading frame initiated at the bacterial RBS. The ligation mixture is then used to transform the E. coli strain M15/rep4 (Qiagen, Inc.) which contains multiple copies of the plasmid pREP4, which expresses the lacI repressor and also confers kanamycin resistance (Kan<sup>r</sup>). Transformants are identified by their ability to grow on LB plates and ampicillin/kanamycin resistant colonies are selected. Plasmid DNA is isolated and confirmed by restriction analysis.

Clones containing the desired constructs are grown overnight (O/N) in liquid culture in LB media supplemented with both Amp (100 ug/ml) and Kan (25 ug/ml). The O/N culture is used to inoculate a large culture at a ratio of 1:100 to 1:250. The cells are grown to an optical density 600 (O.D.<sup>600</sup>) of between 0.4 and 0.6. IPTG

(Isopropyl-B-D-thiogalacto pyranoside) is then added to a final concentration of 1 mM. IPTG induces by inactivating the lacI repressor, clearing the P/O leading to increased gene expression.

Cells are grown for an extra 3 to 4 hours. Cells are then harvested by centrifugation (20 mins at 6000Xg). The cell pellet is solubilized in the chaotropic agent 6 Molar Guanidine HCl by stirring for 3-4 hours at 4°C. The cell debris is removed by centrifugation, and the supernatant containing the polypeptide is loaded onto a nickel-nitrilo-tri-acetic acid ("Ni-NTA") affinity resin column (available from QIAGEN, Inc., *supra*). Proteins with a 6 x His tag bind to the Ni-NTA resin with high affinity and can be purified in a simple one-step procedure (for details see: The QIAexpressionist (1995) QIAGEN, Inc., *supra*).

Briefly, the supernatant is loaded onto the column in 6 M guanidine-HCl, pH 8, the column is first washed with 10 volumes of 6 M guanidine-HCl, pH 8, then washed with 10 volumes of 6 M guanidine-HCl pH 6, and finally the polypeptide is eluted with 6 M guanidine-HCl, pH 5.

The purified protein is then renatured by dialyzing it against phosphate-buffered saline (PBS) or 50 mM Na-acetate, pH 6 buffer plus 200 mM NaCl. Alternatively, the protein can be successfully refolded while immobilized on the Ni-NTA column. The recommended conditions are as follows: renature using a linear 6M-1M urea gradient in 500 mM NaCl, 20% glycerol, 20 mM Tris/HCl pH 7.4, containing protease inhibitors. The renaturation should be performed over a period of 1.5 hours or more. After renaturation the proteins are eluted by the addition of 250 mM imidazole. Imidazole is removed by a final dialyzing step against PBS or 50 mM sodium acetate pH 6 buffer plus 200 mM NaCl. The purified protein is stored at 4°C or frozen at -80°C.

In addition to the above expression vector, the present invention further includes an expression vector comprising phage operator and promoter elements operatively linked to a polynucleotide of the present invention, called pHE4a. (ATCC Accession Number 209645, deposited on February 25, 1998.) This vector contains: 1) a neomycinphosphotransferase gene as a selection marker, 2) an E. coli origin of replication, 3) a T5 phage promoter sequence, 4) two lac operator sequences, 5) a Shine-Delgarno sequence, and 6) the lactose operon repressor gene (lacIq). The origin of replication (oriC) is derived from pUC19 (LTI, Gaithersburg, MD). The promoter sequence and operator sequences are made synthetically.

DNA can be inserted into the pHEa by restricting the vector with NdeI and XbaI, BamHI, XhoI, or Asp718, running the restricted product on a gel, and isolating the larger fragment (the stuffer fragment should be about 310 base pairs). The DNA

insert is generated according to the PCR protocol described in Example 1, using PCR primers having restriction sites for NdeI (5' primer) and XbaI, BamHI, XhoI, or Asp718 (3' primer). The PCR insert is gel purified and restricted with compatible enzymes. The insert and vector are ligated according to standard protocols.

- 5        The engineered vector could easily be substituted in the above protocol to express protein in a bacterial system.

**Example 6: Purification of a Polypeptide from an Inclusion Body**

- 10        The following alternative method can be used to purify a polypeptide expressed in *E. coli* when it is present in the form of inclusion bodies. Unless otherwise specified, all of the following steps are conducted at 4-10°C.

- Upon completion of the production phase of the *E. coli* fermentation, the cell culture is cooled to 4-10°C and the cells harvested by continuous centrifugation at 15,000 rpm (Heraeus Sepatech). On the basis of the expected yield of protein per unit weight of cell paste and the amount of purified protein required, an appropriate amount of cell paste, by weight, is suspended in a buffer solution containing 100 mM Tris, 50 mM EDTA, pH 7.4. The cells are dispersed to a homogeneous suspension using a high shear mixer.

- 20        The cells are then lysed by passing the solution through a microfluidizer (Microfluidics, Corp. or APV Gaulin, Inc.) twice at 4000-6000 psi. The homogenate is then mixed with NaCl solution to a final concentration of 0.5 M NaCl, followed by centrifugation at 7000 xg for 15 min. The resultant pellet is washed again using 0.5M NaCl, 100 mM Tris, 50 mM EDTA, pH 7.4.

- 25        The resulting washed inclusion bodies are solubilized with 1.5 M guanidine hydrochloride (GuHCl) for 2-4 hours. After 7000 xg centrifugation for 15 min., the pellet is discarded and the polypeptide containing supernatant is incubated at 4°C overnight to allow further GuHCl extraction.

- 30        Following high speed centrifugation (30,000 xg) to remove insoluble particles, the GuHCl solubilized protein is refolded by quickly mixing the GuHCl extract with 20 volumes of buffer containing 50 mM sodium, pH 4.5, 150 mM NaCl, 2 mM EDTA by vigorous stirring. The refolded diluted protein solution is kept at 4°C without mixing for 12 hours prior to further purification steps.

      To clarify the refolded polypeptide solution, a previously prepared tangential filtration unit equipped with 0.16 µm membrane filter with appropriate surface area

(e.g., Filtron), equilibrated with 40 mM sodium acetate, pH 6.0 is employed. The filtered sample is loaded onto a cation exchange resin (e.g., Poros HS-50, Perseptive Biosystems). The column is washed with 40 mM sodium acetate, pH 6.0 and eluted with 250 mM, 500 mM, 1000 mM, and 1500 mM NaCl in the same buffer, in a stepwise manner. The absorbance at 280 nm of the effluent is continuously monitored. Fractions are collected and further analyzed by SDS-PAGE.

Fractions containing the polypeptide are then pooled and mixed with 4 volumes of water. The diluted sample is then loaded onto a previously prepared set of tandem columns of strong anion (Poros HQ-50, Perseptive Biosystems) and weak anion (Poros CM-20, Perseptive Biosystems) exchange resins. The columns are equilibrated with 40 mM sodium acetate, pH 6.0. Both columns are washed with 40 mM sodium acetate, pH 6.0, 200 mM NaCl. The CM-20 column is then eluted using a 10 column volume linear gradient ranging from 0.2 M NaCl, 50 mM sodium acetate, pH 6.0 to 1.0 M NaCl, 50 mM sodium acetate, pH 6.5. Fractions are collected under constant  $A_{280}$  monitoring of the effluent. Fractions containing the polypeptide (determined, for instance, by 16% SDS-PAGE) are then pooled.

The resultant polypeptide should exhibit greater than 95% purity after the above refolding and purification steps. No major contaminant bands should be observed from Commaassie blue stained 16% SDS-PAGE gel when 5  $\mu$ g of purified protein is loaded. The purified protein can also be tested for endotoxin/LPS contamination, and typically the LPS content is less than 0.1 ng/ml according to LAL assays.

### **Example 7: Cloning and Expression of a Polypeptide in a Baculovirus**

#### **Expression System**

In this example, the plasmid shuttle vector pA2 is used to insert a polynucleotide into a baculovirus to express a polypeptide. This expression vector contains the strong polyhedrin promoter of the *Autographa californica* nuclear polyhedrosis virus (AcMNPV) followed by convenient restriction sites such as BamHI, Xba I and Asp718. The polyadenylation site of the simian virus 40 ("SV40") is used for efficient polyadenylation. For easy selection of recombinant virus, the plasmid contains the beta-galactosidase gene from *E. coli* under control of a weak *Drosophila* promoter in the same orientation, followed by the polyadenylation signal of the polyhedrin gene. The inserted genes are flanked on both sides by viral sequences for cell-mediated homologous recombination with wild-type viral DNA to generate a viable virus that express the cloned polynucleotide.

Many other baculovirus vectors can be used in place of the vector above, such as pAc373, pVL941, and pAcIM1, as one skilled in the art would readily appreciate, as long as the construct provides appropriately located signals for transcription, translation, secretion and the like, including a signal peptide and an in-frame AUG as required. Such vectors are described, for instance, in Luckow et al., *Virology* 170:31-39 (1989).

Specifically, the cDNA sequence contained in the deposited clone, including the AUG initiation codon and the naturally associated leader sequence identified in Table 1, is amplified using the PCR protocol described in Example 1. If the naturally occurring signal sequence is used to produce the secreted protein, the pA2 vector does not need a second signal peptide. Alternatively, the vector can be modified (pA2 GP) to include a baculovirus leader sequence, using the standard methods described in Summers et al., "A Manual of Methods for Baculovirus Vectors and Insect Cell Culture Procedures," Texas Agricultural Experimental Station Bulletin No. 1555 (1987).

The amplified fragment is isolated from a 1% agarose gel using a commercially available kit ("GeneClean," BIO 101 Inc., La Jolla, Ca.). The fragment then is digested with appropriate restriction enzymes and again purified on a 1% agarose gel.

The plasmid is digested with the corresponding restriction enzymes and optionally, can be dephosphorylated using calf intestinal phosphatase, using routine procedures known in the art. The DNA is then isolated from a 1% agarose gel using a commercially available kit ("GeneClean" BIO 101 Inc., La Jolla, Ca.).

The fragment and the dephosphorylated plasmid are ligated together with T4 DNA ligase. *E. coli* HB101 or other suitable *E. coli* hosts such as XL-1 Blue (Stratagene Cloning Systems, La Jolla, CA) cells are transformed with the ligation mixture and spread on culture plates. Bacteria containing the plasmid are identified by digesting DNA from individual colonies and analyzing the digestion product by gel electrophoresis. The sequence of the cloned fragment is confirmed by DNA sequencing.

Five  $\mu$ g of a plasmid containing the polynucleotide is co-transfected with 1.0  $\mu$ g of a commercially available linearized baculovirus DNA ("BaculoGold™ baculovirus DNA", Pharmingen, San Diego, CA), using the lipofection method described by Felgner et al., *Proc. Natl. Acad. Sci. USA* 84:7413-7417 (1987). One  $\mu$ g of BaculoGold™ virus DNA and 5  $\mu$ g of the plasmid are mixed in a sterile well of a microtiter plate containing 50  $\mu$ l of serum-free Grace's medium (Life Technologies Inc., Gaithersburg, MD). Afterwards, 10  $\mu$ l Lipofectin plus 90  $\mu$ l Grace's medium are added, mixed and incubated for 15 minutes at room temperature. Then the transfection mixture is added drop-wise to Sf9 insect cells (ATCC CRL 1711) seeded in a 35 mm

tissue culture plate with 1 ml Grace's medium without serum. The plate is then incubated for 5 hours at 27° C. The transfection solution is then removed from the plate and 1 ml of Grace's insect medium supplemented with 10% fetal calf serum is added. Cultivation is then continued at 27° C for four days.

- 5       After four days the supernatant is collected and a plaque assay is performed, as described by Summers and Smith, *supra*. An agarose gel with "Blue Gal" (Life Technologies Inc., Gaithersburg) is used to allow easy identification and isolation of gal-expressing clones, which produce blue-stained plaques. (A detailed description of a "plaque assay" of this type can also be found in the user's guide for insect cell culture and baculovirology distributed by Life Technologies Inc., Gaithersburg, page 9-10.)
- 10       After appropriate incubation, blue stained plaques are picked with the tip of a micropipettor (e.g., Eppendorf). The agar containing the recombinant viruses is then resuspended in a microcentrifuge tube containing 200 µl of Grace's medium and the suspension containing the recombinant baculovirus is used to infect Sf9 cells seeded in
- 15       35 mm dishes. Four days later the supernatants of these culture dishes are harvested and then they are stored at 4° C.

- To verify the expression of the polypeptide, Sf9 cells are grown in Grace's medium supplemented with 10% heat-inactivated FBS. The cells are infected with the recombinant baculovirus containing the polynucleotide at a multiplicity of infection
- 20       ("MOI") of about 2. If radiolabeled proteins are desired, 6 hours later the medium is removed and is replaced with SF900 II medium minus methionine and cysteine (available from Life Technologies Inc., Rockville, MD). After 42 hours, 5 µCi of <sup>35</sup>S-methionine and 5 µCi <sup>35</sup>S-cysteine (available from Amersham) are added. The cells are further incubated for 16 hours and then are harvested by centrifugation. The proteins
- 25       in the supernatant as well as the intracellular proteins are analyzed by SDS-PAGE followed by autoradiography (if radiolabeled).

Microsequencing of the amino acid sequence of the amino terminus of purified protein may be used to determine the amino terminal sequence of the produced protein.

### 30       Example 8: Expression of a Polypeptide in Mammalian Cells

The polypeptide of the present invention can be expressed in a mammalian cell. A typical mammalian expression vector contains a promoter element, which mediates

the initiation of transcription of mRNA, a protein coding sequence, and signals required for the termination of transcription and polyadenylation of the transcript. Additional elements include enhancers, Kozak sequences and intervening sequences flanked by donor and acceptor sites for RNA splicing. Highly efficient transcription is achieved with the early and late promoters from SV40, the long terminal repeats (LTRs) from Retroviruses, e.g., RSV, HTLVI, HIVI and the early promoter of the cytomegalovirus (CMV). However, cellular elements can also be used (e.g., the human actin promoter).

Suitable expression vectors for use in practicing the present invention include, for example, vectors such as pSVL and pMSG (Pharmacia, Uppsala, Sweden), pRSVcat (ATCC 37152), pSV2dhfr (ATCC 37146), pBC12MI (ATCC 67109), pCMVSPORT 2.0, and pCMVSPORT 3.0. Mammalian host cells that could be used include, human Hela, 293, H9 and Jurkat cells, mouse NIH3T3 and C127 cells, Cos 1, Cos 7 and CV1, quail QC1-3 cells, mouse L cells and Chinese hamster ovary (CHO) cells.

Alternatively, the polypeptide can be expressed in stable cell lines containing the polynucleotide integrated into a chromosome. The co-transfection with a selectable marker such as dhfr, gpt, neomycin, hygromycin allows the identification and isolation of the transfected cells.

The transfected gene can also be amplified to express large amounts of the encoded protein. The DHFR (dihydrofolate reductase) marker is useful in developing cell lines that carry several hundred or even several thousand copies of the gene of interest. (See, e.g., Alt, F. W., et al., J. Biol. Chem. 253:1357-1370 (1978); Hamlin, J. L. and Ma, C., Biochem. et Biophys. Acta, 1097:107-143 (1990); Page, M. J. and Sydenham, M. A., Biotechnology 9:64-68 (1991).) Another useful selection marker is the enzyme glutamine synthase (GS) (Murphy et al., Biochem J. 227:277-279 (1991); Bebbington et al., Bio/Technology 10:169-175 (1992). Using these markers, the mammalian cells are grown in selective medium and the cells with the highest resistance are selected. These cell lines contain the amplified gene(s) integrated into a chromosome. Chinese hamster ovary (CHO) and NSO cells are often used for the production of proteins.

Derivatives of the plasmid pSV2-dhfr (ATCC Accession No. 37146), the expression vectors pC4 (ATCC Accession No. 209646) and pC6 (ATCC Accession No. 209647) contain the strong promoter (LTR) of the Rous Sarcoma Virus (Cullen et al., Molecular and Cellular Biology, 438-447 (March, 1985)) plus a fragment of the CMV-enhancer (Boshart et al., Cell 41:521-530 (1985).) Multiple cloning sites, e.g., with the restriction enzyme cleavage sites BamHI, XbaI and Asp718, facilitate the cloning of the gene of interest. The vectors also contain the 3' intron, the



polyadenylation and termination signal of the rat preproinsulin gene, and the mouse DHFR gene under control of the SV40 early promoter.

Specifically, the plasmid pC6, for example, is digested with appropriate restriction enzymes and then dephosphorylated using calf intestinal phosphates by procedures known in the art. The vector is then isolated from a 1% agarose gel.

A polynucleotide of the present invention is amplified according to the protocol outlined in Example 1. If the naturally occurring signal sequence is used to produce the secreted protein, the vector does not need a second signal peptide. Alternatively, if the naturally occurring signal sequence is not used, the vector can be modified to include a heterologous signal sequence. (See, e.g., WO 96/34891.)

The amplified fragment is isolated from a 1% agarose gel using a commercially available kit ("GeneClean," BIO 101 Inc., La Jolla, Ca.). The fragment then is digested with appropriate restriction enzymes and again purified on a 1% agarose gel.

The amplified fragment is then digested with the same restriction enzyme and purified on a 1% agarose gel. The isolated fragment and the dephosphorylated vector are then ligated with T4 DNA ligase. *E. coli* HB101 or XL-1 Blue cells are then transformed and bacteria are identified that contain the fragment inserted into plasmid pC6 using, for instance, restriction enzyme analysis.

Chinese hamster ovary cells lacking an active DHFR gene is used for transfection. Five  $\mu$ g of the expression plasmid pC6 is cotransfected with 0.5  $\mu$ g of the plasmid pSVneo using lipofectin (Felgner et al., *supra*). The plasmid pSV2-neo contains a dominant selectable marker, the *neo* gene from Tn5 encoding an enzyme that confers resistance to a group of antibiotics including G418. The cells are seeded in alpha minus MEM supplemented with 1 mg/ml G418. After 2 days, the cells are trypsinized and seeded in hybridoma cloning plates (Greiner, Germany) in alpha minus MEM supplemented with 10, 25, or 50 ng/ml of methotrexate plus 1 mg/ml G418. After about 10-14 days single clones are trypsinized and then seeded in 6-well petri dishes or 10 ml flasks using different concentrations of methotrexate (50 nM, 100 nM, 200 nM, 400 nM, 800 nM). Clones growing at the highest concentrations of methotrexate are then transferred to new 6-well plates containing even higher concentrations of methotrexate (1  $\mu$ M, 2  $\mu$ M, 5  $\mu$ M, 10 mM, 20 mM). The same procedure is repeated until clones are obtained which grow at a concentration of 100 - 200  $\mu$ M. Expression of the desired gene product is analyzed, for instance, by SDS-PAGE and Western blot or by reversed phase HPLC analysis.

#### **Example 9: Protein Fusions**

The polypeptides of the present invention are preferably fused to other proteins. These fusion proteins can be used for a variety of applications. For example, fusion of the present polypeptides to His-tag, HA-tag, protein A, IgG domains, and maltose binding protein facilitates purification. (See Example 5; see also EP A 394,827; Traunecker, et al., Nature 331:84-86 (1988).) Similarly, fusion to IgG-1, IgG-3, and albumin increases the half-life time in vivo. Nuclear localization signals fused to the polypeptides of the present invention can target the protein to a specific subcellular localization, while covalent heterodimer or homodimers can increase or decrease the activity of a fusion protein. Fusion proteins can also create chimeric molecules having more than one function. Finally, fusion proteins can increase solubility and/or stability of the fused protein compared to the non-fused protein. All of the types of fusion proteins described above can be made by modifying the following protocol, which outlines the fusion of a polypeptide to an IgG molecule, or the protocol described in Example 5.

Briefly, the human Fc portion of the IgG molecule can be PCR amplified, using primers that span the 5' and 3' ends of the sequence described below. These primers also should have convenient restriction enzyme sites that will facilitate cloning into an expression vector, preferably a mammalian expression vector.

For example, if pC4 (Accession No. 209646) is used, the human Fc portion can be ligated into the BamHI cloning site. Note that the 3' BamHI site should be destroyed. Next, the vector containing the human Fc portion is re-restricted with BamHI, linearizing the vector, and a polynucleotide of the present invention, isolated by the PCR protocol described in Example 1, is ligated into this BamHI site. Note that the polynucleotide is cloned without a stop codon, otherwise a fusion protein will not be produced.

If the naturally occurring signal sequence is used to produce the secreted protein, pC4 does not need a second signal peptide. Alternatively, if the naturally occurring signal sequence is not used, the vector can be modified to include a heterologous signal sequence. (See, e.g., WO 96/34891.)

Human IgG Fc region:

```
GGGATCCGGAGCCCAAATCTTCTGACAAAACTCACACATGCCCACCGTGCC
CAGCACCTGAATTCGAGGGTGCACCGTCAGTCTTCCTCTTCCCCCAAACC
CAAGGACACCCTCATGATCTCCCGGACTCCTGAGGTCACATGCGTGGTGGT
GGACGTAAGCCACGAAGACCCTGAGGTCAAGTTCAACTGGTACGTGGACG
GCGTGGAGGTGCATAATGCCAAGACAAAGCCGCGGGAGGAGCAGTACAAC
AGCACGTACCGTGTGGTCAGCGTCCTCACCGTCCTGCACCAGGACTGGCTG
```

AATGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGCCCTCCCAACCCCC  
ATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAACCACAGGT  
GTACACCCTGCCCCCATCCCGGGATGAGCTGACCAAGAACCAGGTCAGCCT  
GACCTGCCTGGTCAAAGGCTTCTATCCAAGCGACATCGCCGTGGAGTGGGA  
5 GAGCAATGGGCAGCCGGAGAACAACACTACAAGACCACGCCTCCCGTGCTGG  
ACTCCGACGGCTCCTTCTTCCTCTACAGCAAGCTCACCGTGGACAAGAGCA  
GGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCATGAGGCTCTGC  
ACAACCACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAATGAGTGC  
GACGGCCGCGACTCTAGAGGAT (SEQ ID NO:1)

10

**Example 10: Production of an Antibody from a Polypeptide**

The antibodies of the present invention can be prepared by a variety of methods. (See, Current Protocols, Chapter 2.) For example, cells expressing a polypeptide of the present invention is administered to an animal to induce the production of sera  
15 containing polyclonal antibodies. In a preferred method, a preparation of the secreted protein is prepared and purified to render it substantially free of natural contaminants. Such a preparation is then introduced into an animal in order to produce polyclonal antisera of greater specific activity.

In the most preferred method, the antibodies of the present invention are  
20 monoclonal antibodies (or protein binding fragments thereof). Such monoclonal antibodies can be prepared using hybridoma technology. (Köhler et al., Nature 256:495 (1975); Köhler et al., Eur. J. Immunol. 6:511 (1976); Köhler et al., Eur. J. Immunol. 6:292 (1976); Hammerling et al., in: Monoclonal Antibodies and T-Cell Hybridomas, Elsevier, N.Y., pp. 563-681 (1981).) In general, such procedures  
25 involve immunizing an animal (preferably a mouse) with polypeptide or, more preferably, with a secreted polypeptide-expressing cell. Such cells may be cultured in any suitable tissue culture medium; however, it is preferable to culture cells in Earle's modified Eagle's medium supplemented with 10% fetal bovine serum (inactivated at about 56°C), and supplemented with about 10 g/l of nonessential amino acids, about  
30 1,000 U/ml of penicillin, and about 100 µg/ml of streptomycin.

The splenocytes of such mice are extracted and fused with a suitable myeloma cell line. Any suitable myeloma cell line may be employed in accordance with the present invention; however, it is preferable to employ the parent myeloma cell line (SP2O), available from the ATCC. After fusion, the resulting hybridoma cells are  
35 selectively maintained in HAT medium, and then cloned by limiting dilution as described by Wands et al. (Gastroenterology 80:225-232 (1981).) The hybridoma cells

obtained through such a selection are then assayed to identify clones which secrete antibodies capable of binding the polypeptide.

Alternatively, additional antibodies capable of binding to the polypeptide can be produced in a two-step procedure using anti-idiotypic antibodies. Such a method makes use of the fact that antibodies are themselves antigens, and therefore, it is possible to obtain an antibody which binds to a second antibody. In accordance with this method, protein specific antibodies are used to immunize an animal, preferably a mouse. The splenocytes of such an animal are then used to produce hybridoma cells, and the hybridoma cells are screened to identify clones which produce an antibody whose ability to bind to the protein-specific antibody can be blocked by the polypeptide. Such antibodies comprise anti-idiotypic antibodies to the protein-specific antibody and can be used to immunize an animal to induce formation of further protein-specific antibodies.

It will be appreciated that Fab and F(ab')<sub>2</sub> and other fragments of the antibodies of the present invention may be used according to the methods disclosed herein. Such fragments are typically produced by proteolytic cleavage, using enzymes such as papain (to produce Fab fragments) or pepsin (to produce F(ab')<sub>2</sub> fragments). Alternatively, secreted protein-binding fragments can be produced through the application of recombinant DNA technology or through synthetic chemistry.

For in vivo use of antibodies in humans, it may be preferable to use "humanized" chimeric monoclonal antibodies. Such antibodies can be produced using genetic constructs derived from hybridoma cells producing the monoclonal antibodies described above. Methods for producing chimeric antibodies are known in the art. (See, for review, Morrison, Science 229:1202 (1985); Oi et al., BioTechniques 4:214 (1986); Cabilly et al., U.S. Patent No. 4,816,567; Taniguchi et al., EP 171496; Morrison et al., EP 173494; Neuberger et al., WO 8601533; Robinson et al., WO 8702671; Boulianne et al., Nature 312:643 (1984); Neuberger et al., Nature 314:268 (1985).)

### **Example 11: Production Of Secreted Protein For High-Throughput Screening Assays**

The following protocol produces a supernatant containing a polypeptide to be tested. This supernatant can then be used in the Screening Assays described in Examples 13-20.

First, dilute Poly-D-Lysine (644 587 Boehringer-Mannheim) stock solution (1mg/ml in PBS) 1:20 in PBS (w/o calcium or magnesium 17-516F Biowhittaker) for a working solution of 50ug/ml. Add 200 ul of this solution to each well (24 well plates)

and incubate at RT for 20 minutes. Be sure to distribute the solution over each well (note: a 12-channel pipetter may be used with tips on every other channel). Aspirate off the Poly-D-Lysine solution and rinse with 1ml PBS (Phosphate Buffered Saline). The PBS should remain in the well until just prior to plating the cells and plates may be poly-lysine coated in advance for up to two weeks.

5 Plate 293T cells (do not carry cells past P+20) at  $2 \times 10^5$  cells/well in .5ml DMEM(Dulbecco's Modified Eagle Medium)(with 4.5 G/L glucose and L-glutamine (12-604F Biowhittaker))/10% heat inactivated FBS(14-503F Biowhittaker)/1x Penstrep(17-602E Biowhittaker). Let the cells grow overnight.

10 The next day, mix together in a sterile solution basin: 300 ul Lipofectamine (18324-012 Gibco/BRL) and 5ml Optimem I (31985070 Gibco/BRL)/96-well plate. With a small volume multi-channel pipetter, aliquot approximately 2ug of an expression vector containing a polynucleotide insert, produced by the methods described in Examples 8 or 9, into an appropriately labeled 96-well round bottom plate. With a multi-channel pipetter, add 50ul of the Lipofectamine/Optimem I mixture to each well. Pipette up and down gently to mix. Incubate at RT 15-45 minutes. After about 20 minutes, use a multi-channel pipetter to add 150ul Optimem I to each well. As a control, one plate of vector DNA lacking an insert should be transfected with each set of transfections.

20 Preferably, the transfection should be performed by tag-teaming the following tasks. By tag-teaming, hands on time is cut in half, and the cells do not spend too much time on PBS. First, person A aspirates off the media from four 24-well plates of cells, and then person B rinses each well with .5-1ml PBS. Person A then aspirates off PBS rinse, and person B, using a 12-channel pipetter with tips on every other channel, adds the 200ul of DNA/Lipofectamine/Optimem I complex to the odd wells first, then to the even wells, to each row on the 24-well plates. Incubate at 37°C for 6 hours.

30 While cells are incubating, prepare appropriate media, either 1%BSA in DMEM with 1x penstrep, or CHO-5 media (116.6 mg/L of  $\text{CaCl}_2$  (anhyd); 0.00130 mg/L  $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$ ; 0.050 mg/L of  $\text{Fe}(\text{NO}_3)_3 \cdot 9\text{H}_2\text{O}$ ; 0.417 mg/L of  $\text{FeSO}_4 \cdot 7\text{H}_2\text{O}$ ; 311.80 mg/L of KCl; 28.64 mg/L of  $\text{MgCl}_2$ ; 48.84 mg/L of  $\text{MgSO}_4$ ; 6995.50 mg/L of NaCl; 2400.0 mg/L of  $\text{NaHCO}_3$ ; 62.50 mg/L of  $\text{NaH}_2\text{PO}_4 \cdot \text{H}_2\text{O}$ ; 71.02 mg/L of  $\text{Na}_2\text{HPO}_4$ ; .4320 mg/L of  $\text{ZnSO}_4 \cdot 7\text{H}_2\text{O}$ ; .002 mg/L of Arachidonic Acid ; 1.022 mg/L of Cholesterol; .070 mg/L of DL-alpha-Tocopherol-Acetate; 0.0520 mg/L of Linoleic Acid; 0.010 mg/L of Linolenic Acid; 0.010 mg/L of Myristic Acid; 0.010 mg/L of Oleic Acid; 0.010 mg/L of Palmitric Acid; 0.010 mg/L of Palmitic Acid; 100 mg/L of Pluronic F-68; 0.010 mg/L of Stearic Acid; 2.20 mg/L of Tween 80; 4551 mg/L of D-

Glucose; 130.85 mg/ml of L- Alanine; 147.50 mg/ml of L-Arginine-HCL; 7.50 mg/ml of L-Asparagine-H<sub>2</sub>O; 6.65 mg/ml of L-Aspartic Acid; 29.56 mg/ml of L-Cystine-2HCL-H<sub>2</sub>O; 31.29 mg/ml of L-Cystine-2HCL; 7.35 mg/ml of L-Glutamic Acid; 365.0 mg/ml of L-Glutamine; 18.75 mg/ml of Glycine; 52.48 mg/ml of L-Histidine-HCL-H<sub>2</sub>O; 106.97 mg/ml of L-Isoleucine; 111.45 mg/ml of L-Leucine; 163.75 mg/ml of L-Lysine HCL; 32.34 mg/ml of L-Methionine; 68.48 mg/ml of L-Phenylalanine; 40.0 mg/ml of L-Proline; 26.25 mg/ml of L-Serine; 101.05 mg/ml of L-Threonine; 19.22 mg/ml of L-Tryptophan; 91.79 mg/ml of L-Tyrosine-2Na-2H<sub>2</sub>O; 99.65 mg/ml of L-Valine; 0.0035 mg/L of Biotin; 3.24 mg/L of D-Ca Pantothenate; 11.78 mg/L of Choline Chloride; 4.65 mg/L of Folic Acid; 15.60 mg/L of i-Inositol; 3.02 mg/L of Niacinamide; 3.00 mg/L of Pyridoxal HCL; 0.031 mg/L of Pyridoxine HCL; 0.319 mg/L of Riboflavin; 3.17 mg/L of Thiamine HCL; 0.365 mg/L of Thymidine; and 0.680 mg/L of Vitamin B<sub>12</sub>; 25 mM of HEPES Buffer; 2.39 mg/L of Na Hypoxanthine; 0.105 mg/L of Lipoic Acid; 0.081 mg/L of Sodium Putrescine-2HCL; 55.0 mg/L of Sodium Pyruvate; 0.0067 mg/L of Sodium Selenite; 20uM of Ethanolamine; 0.122 mg/L of Ferric Citrate; 41.70 mg/L of Methyl-B-Cyclodextrin complexed with Linoleic Acid; 33.33 mg/L of Methyl-B-Cyclodextrin complexed with Oleic Acid; and 10 mg/L of Methyl-B-Cyclodextrin complexed with Retinal) with 2mm glutamine and 1x penstrep. (BSA (81-068-3 Bayer) 100gm dissolved in 1L DMEM for a 10% BSA stock solution). Filter the media and collect 50 ul for endotoxin assay in 15ml polystyrene conical.

The transfection reaction is terminated, preferably by tag-teaming, at the end of the incubation period. Person A aspirates off the transfection media, while person B adds 1.5ml appropriate media to each well. Incubate at 37°C for 45 or 72 hours depending on the media used: 1%BSA for 45 hours or CHO-5 for 72 hours.

On day four, using a 300ul multichannel pipetter, aliquot 600ul in one 1ml deep well plate and the remaining supernatant into a 2ml deep well. The supernatants from each well can then be used in the assays described in Examples 13-20.

It is specifically understood that when activity is obtained in any of the assays described below using a supernatant, the activity originates from either the polypeptide directly (e.g., as a secreted protein) or by the polypeptide inducing expression of other proteins, which are then secreted into the supernatant. Thus, the invention further provides a method of identifying the protein in the supernatant characterized by an activity in a particular assay.

#### **Example 12: Construction of GAS Reporter Construct**

One signal transduction pathway involved in the differentiation and proliferation of cells is called the Jaks-STATs pathway. Activated proteins in the Jaks-STATs pathway bind to gamma activation site "GAS" elements or interferon-sensitive responsive element ("ISRE"), located in the promoter of many genes. The binding of a protein to these elements alter the expression of the associated gene.

GAS and ISRE elements are recognized by a class of transcription factors called Signal Transducers and Activators of Transcription, or "STATs." There are six members of the STATs family. Stat1 and Stat3 are present in many cell types, as is Stat2 (as response to IFN-alpha is widespread). Stat4 is more restricted and is not in many cell types though it has been found in T helper class I, cells after treatment with IL-12. Stat5 was originally called mammary growth factor, but has been found at higher concentrations in other cells including myeloid cells. It can be activated in tissue culture cells by many cytokines.

The STATs are activated to translocate from the cytoplasm to the nucleus upon tyrosine phosphorylation by a set of kinases known as the Janus Kinase ("Jaks") family. Jaks represent a distinct family of soluble tyrosine kinases and include Tyk2, Jak1, Jak2, and Jak3. These kinases display significant sequence similarity and are generally catalytically inactive in resting cells.

The Jaks are activated by a wide range of receptors summarized in the Table below. (Adapted from review by Schidler and Darnell, Ann. Rev. Biochem. 64:621-51 (1995).) A cytokine receptor family, capable of activating Jaks, is divided into two groups: (a) Class 1 includes receptors for IL-2, IL-3, IL-4, IL-6, IL-7, IL-9, IL-11, IL-12, IL-15, Epo, PRL, GH, G-CSF, GM-CSF, LIF, CNTF, and thrombopoietin; and (b) Class 2 includes IFN-a, IFN-g, and IL-10. The Class 1 receptors share a conserved cysteine motif (a set of four conserved cysteines and one tryptophan) and a WSXWS motif (a membrane proximal region encoding Trp-Ser-Xxx-Trp-Ser (SEQ ID NO:2)).

Thus, on binding of a ligand to a receptor, Jaks are activated, which in turn activate STATs, which then translocate and bind to GAS elements. This entire process is encompassed in the Jaks-STATs signal transduction pathway.

Therefore, activation of the Jaks-STATs pathway, reflected by the binding of the GAS or the ISRE element, can be used to indicate proteins involved in the proliferation and differentiation of cells. For example, growth factors and cytokines are known to activate the Jaks-STATs pathway. (See Table below.) Thus, by using GAS elements linked to reporter molecules, activators of the Jaks-STATs pathway can be identified.

	<u>Ligand</u>	<u>tyk2</u>	<u>JAKs</u> <u>Jak1</u>	<u>Jak2</u>	<u>Jak3</u>	<u>STATS</u>	<u>GAS(elements) or ISRE</u>
<u>IFN family</u>							
5	IFN-a/B	+	+	-	-	1,2,3	ISRE
	IFN-g		+	+	-	1	GAS (IRF1>Lys6>IFP)
	Il-10	+	?	?	-	1,3	
<u>gp130 family</u>							
10	IL-6 (Pleiotrohic)	+	+	+	?	1,3	GAS (IRF1>Lys6>IFP)
	Il-11(Pleiotrohic)	?	+	?	?	1,3	
	OnM(Pleiotrohic)	?	+	+	?	1,3	
	LIF(Pleiotrohic)	?	+	+	?	1,3	
	CNTF(Pleiotrohic)	-/+	+	+	?	1,3	
15	G-CSF(Pleiotrohic)	?	+	?	?	1,3	
	IL-12(Pleiotrohic)	+	-	+	+	1,3	
<u>g-C family</u>							
20	IL-2 (lymphocytes)	-	+	-	+	1,3,5	GAS
	IL-4 (lymph/myeloid)	-	+	-	+	6	GAS (IRF1 = IFP >>Ly6)(IgH)
	IL-7 (lymphocytes)	-	+	-	+	5	GAS
	IL-9 (lymphocytes)	-	+	-	+	5	GAS
	IL-13 (lymphocyte)	-	+	?	?	6	GAS
	IL-15	?	+	?	+	5	GAS
25							
<u>gp140 family</u>							
	IL-3 (myeloid)	-	-	+	-	5	GAS (IRF1>IFP>>Ly6)
	IL-5 (myeloid)	-	-	+	-	5	GAS
	GM-CSF (myeloid)	-	-	+	-	5	GAS
30							
<u>Growth hormone family</u>							
	GH	?	-	+	-	5	
	PRL	?	+/-	+	-	1,3,5	
	EPO	?	-	+	-	5	GAS(B-CAS>IRF1=IFP>>Ly6)
35							
<u>Receptor Tyrosine Kinases</u>							
	EGF	?	+	+	-	1,3	GAS (IRF1)
	PDGF	?	+	+	-	1,3	
	CSF-1	?	+	+	-	1,3	GAS (not IRF1)



To construct a synthetic GAS containing promoter element, which is used in the Biological Assays described in Examples 13-14, a PCR based strategy is employed to generate a GAS-SV40 promoter sequence. The 5' primer contains four tandem copies of the GAS binding site found in the IRF1 promoter and previously demonstrated to bind STATs upon induction with a range of cytokines (Rothman et al., Immunity 1:457-468 (1994).), although other GAS or ISRE elements can be used instead. The 5' primer also contains 18bp of sequence complementary to the SV40 early promoter sequence and is flanked with an XhoI site. The sequence of the 5' primer is:

5':GCGCCTCGAGATTTCCTCCGAAATCTAGATTTCCTCCGAAATGATTTCCTCCG  
AAATGATTTCCTCCGAAATATCTGCCATCTCAATTAG:3' (SEQ ID NO:3)

The downstream primer is complementary to the SV40 promoter and is flanked with a Hind III site: 5':GCGGCAAGCTTTTGTCAAAGCCTAGGC:3' (SEQ ID NO:4)

PCR amplification is performed using the SV40 promoter template present in the B-gal:promoter plasmid obtained from Clontech. The resulting PCR fragment is digested with XhoI/Hind III and subcloned into BLSK2-. (Stratagene.) Sequencing with forward and reverse primers confirms that the insert contains the following sequence:

5':CTCGAGATTTCCTCCGAAATCTAGATTTCCTCCGAAATGATTTCCTCCGAAATG  
ATTTTCCTCCGAAATATCTGCCATCTCAATTAGTCAGCAACCATAGTCCCGCCC  
CTAACTCCGCCCATCCCGCCCCTAACTCCGCCCAGTTCGCCCATTCTCCGC  
CCCATGGCTGACTAATTTTTTTTATTTATGCAGAGGCCGAGGCCGCTCGGC  
CTCTGAGCTATTCCAGAAGTAGTGAGGAGGCTTTTTTGGAGGCCTAGGCTTT  
TGCAAAAAGCTT:3' (SEQ ID NO:5)

With this GAS promoter element linked to the SV40 promoter, a GAS:SEAP2 reporter construct is next engineered. Here, the reporter molecule is a secreted alkaline phosphatase, or "SEAP." Clearly, however, any reporter molecule can be instead of SEAP, in this or in any of the other Examples. Well known reporter molecules that can be used instead of SEAP include chloramphenicol acetyltransferase (CAT), luciferase, alkaline phosphatase, B-galactosidase, green fluorescent protein (GFP), or any protein detectable by an antibody.

The above sequence confirmed synthetic GAS-SV40 promoter element is subcloned into the pSEAP-Promoter vector obtained from Clontech using HindIII and XhoI, effectively replacing the SV40 promoter with the amplified GAS:SV40 promoter element, to create the GAS-SEAP vector. However, this vector does not contain a neomycin resistance gene, and therefore, is not preferred for mammalian expression systems.

Thus, in order to generate mammalian stable cell lines expressing the GAS-SEAP reporter, the GAS-SEAP cassette is removed from the GAS-SEAP vector using SalI and NotI, and inserted into a backbone vector containing the neomycin resistance gene, such as pGFP-1 (Clontech), using these restriction sites in the multiple cloning  
5 site, to create the GAS-SEAP/Neo vector. Once this vector is transfected into mammalian cells, this vector can then be used as a reporter molecule for GAS binding as described in Examples 13-14.

Other constructs can be made using the above description and replacing GAS with a different promoter sequence. For example, construction of reporter molecules  
10 containing NFK-B and EGR promoter sequences are described in Examples 15 and 16. However, many other promoters can be substituted using the protocols described in these Examples. For instance, SRE, IL-2, NFAT, or Osteocalcin promoters can be substituted, alone or in combination (e.g., GAS/NF-KB/EGR, GAS/NF-KB, IL-2/NFAT, or NF-KB/GAS). Similarly, other cell lines can be used to test reporter  
15 construct activity, such as HELA (epithelial), HUVEC (endothelial), Reh (B-cell), Saos-2 (osteoblast), HUVAC (aortic), or Cardiomyocyte.

**Example 13: High-Throughput Screening Assay for T-cell Activity.**

The following protocol is used to assess T-cell activity by identifying factors,  
20 such as growth factors and cytokines, that may proliferate or differentiate T-cells. T-cell activity is assessed using the GAS/SEAP/Neo construct produced in Example 12. Thus, factors that increase SEAP activity indicate the ability to activate the Jaks-STATS signal transduction pathway. The T-cell used in this assay is Jurkat T-cells (ATCC Accession No. TIB-152), although Molt-3 cells (ATCC Accession No. CRL-1552) and  
25 Molt-4 cells (ATCC Accession No. CRL-1582) cells can also be used.

Jurkat T-cells are lymphoblastic CD4+ Th1 helper cells. In order to generate stable cell lines, approximately 2 million Jurkat cells are transfected with the GAS-SEAP/neo vector using DMRIE-C (Life Technologies)(transfection procedure described below). The transfected cells are seeded to a density of approximately  
30 20,000 cells per well and transfectants resistant to 1 mg/ml gentamicin selected. Resistant colonies are expanded and then tested for their response to increasing concentrations of interferon gamma. The dose response of a selected clone is demonstrated.

Specifically, the following protocol will yield sufficient cells for 75 wells containing 200 ul of cells. Thus, it is either scaled up, or performed in multiple to  
35 generate sufficient cells for multiple 96 well plates. Jurkat cells are maintained in RPMI + 10% serum with 1%Pen-Strep. Combine 2.5 mls of OPTI-MEM (Life Technologies)

with 10 ug of plasmid DNA in a T25 flask. Add 2.5 ml OPTI-MEM containing 50 ul of DMRIE-C and incubate at room temperature for 15-45 mins.

During the incubation period, count cell concentration, spin down the required number of cells ( $10^7$  per transfection), and resuspend in OPTI-MEM to a final  
5 concentration of  $10^7$  cells/ml. Then add 1ml of  $1 \times 10^7$  cells in OPTI-MEM to T25 flask and incubate at 37°C for 6 hrs. After the incubation, add 10 ml of RPMI + 15% serum.

The Jurkat:GAS-SEAP stable reporter lines are maintained in RPMI + 10% serum, 1 mg/ml Gentamicin, and 1% Pen-Strep. These cells are treated with supernatants containing a polypeptide as produced by the protocol described in Example 11.

10 On the day of treatment with the supernatant, the cells should be washed and resuspended in fresh RPMI + 10% serum to a density of 500,000 cells per ml. The exact number of cells required will depend on the number of supernatants being screened. For one 96 well plate, approximately 10 million cells (for 10 plates, 100 million cells) are required.

15 Transfer the cells to a triangular reservoir boat, in order to dispense the cells into a 96 well dish, using a 12 channel pipette. Using a 12 channel pipette, transfer 200 ul of cells into each well (therefore adding 100, 000 cells per well).

After all the plates have been seeded, 50 ul of the supernatants are transferred directly from the 96 well plate containing the supernatants into each well using a 12  
20 channel pipette. In addition, a dose of exogenous interferon gamma (0.1, 1.0, 10 ng) is added to wells H9, H10, and H11 to serve as additional positive controls for the assay.

The 96 well dishes containing Jurkat cells treated with supernatants are placed in an incubator for 48 hrs (note: this time is variable between 48-72 hrs). 35 ul samples  
25 from each well are then transferred to an opaque 96 well plate using a 12 channel pipette. The opaque plates should be covered (using sellophane covers) and stored at -20°C until SEAP assays are performed according to Example 17. The plates containing the remaining treated cells are placed at 4°C and serve as a source of material for repeating the assay on a specific well if desired.

30 As a positive control, 100 Unit/ml interferon gamma can be used which is known to activate Jurkat T cells. Over 30 fold induction is typically observed in the positive control wells.

35 **Example 14: High-Throughput Screening Assay Identifying Myeloid Activity**

The following protocol is used to assess myeloid activity by identifying factors, such as growth factors and cytokines, that may proliferate or differentiate myeloid cells. Myeloid cell activity is assessed using the GAS/SEAP/Neo construct produced in Example 12. Thus, factors that increase SEAP activity indicate the ability to activate the Jaks-STATS signal transduction pathway. The myeloid cell used in this assay is U937, a pre-monocyte cell line, although TF-1, HL60, or KG1 can be used.

To transiently transfect U937 cells with the GAS/SEAP/Neo construct produced in Example 12, a DEAE-Dextran method (Kharbanda et. al., 1994, Cell Growth & Differentiation, 5:259-265) is used. First, harvest  $2 \times 10^7$  U937 cells and wash with PBS. The U937 cells are usually grown in RPMI 1640 medium containing 10% heat-inactivated fetal bovine serum (FBS) supplemented with 100 units/ml penicillin and 100 mg/ml streptomycin.

Next, suspend the cells in 1 ml of 20 mM Tris-HCl (pH 7.4) buffer containing 0.5 mg/ml DEAE-Dextran, 8 ug GAS-SEAP2 plasmid DNA, 140 mM NaCl, 5 mM KCl, 375 uM  $\text{Na}_2\text{HPO}_4 \cdot 7\text{H}_2\text{O}$ , 1 mM  $\text{MgCl}_2$ , and 675 uM  $\text{CaCl}_2$ . Incubate at 37°C for 45 min.

Wash the cells with RPMI 1640 medium containing 10% FBS and then resuspend in 10 ml complete medium and incubate at 37°C for 36 hr.

The GAS-SEAP/U937 stable cells are obtained by growing the cells in 400 ug/ml G418. The G418-free medium is used for routine growth but every one to two months, the cells should be re-grown in 400 ug/ml G418 for couple of passages.

These cells are tested by harvesting  $1 \times 10^8$  cells (this is enough for ten 96-well plates assay) and wash with PBS. Suspend the cells in 200 ml above described growth medium, with a final density of  $5 \times 10^5$  cells/ml. Plate 200 ul cells per well in the 96-well plate (or  $1 \times 10^5$  cells/well).

Add 50 ul of the supernatant prepared by the protocol described in Example 11. Incubate at 37°C for 48 to 72 hr. As a positive control, 100 Unit/ml interferon gamma can be used which is known to activate U937 cells. Over 30 fold induction is typically observed in the positive control wells. SEAP assay the supernatant according to the protocol described in Example 17.

#### **Example 15: High-Throughput Screening Assay Identifying Neuronal Activity.**

When cells undergo differentiation and proliferation, a group of genes are activated through many different signal transduction pathways. One of these genes, EGR1 (early growth response gene 1), is induced in various tissues and cell types upon

activation. The promoter of EGR1 is responsible for such induction. Using the EGR1 promoter linked to reporter molecules, activation of cells can be assessed.

Particularly, the following protocol is used to assess neuronal activity in PC12 cell lines. PC12 cells (rat phenochromocytoma cells) are known to proliferate and/or  
5 differentiate by activation with a number of mitogens, such as TPA (tetradecanoyl phorbol acetate), NGF (nerve growth factor), and EGF (epidermal growth factor). The EGR1 gene expression is activated during this treatment. Thus, by stably transfecting PC12 cells with a construct containing an EGR promoter linked to SEAP reporter, activation of PC12 cells can be assessed.

10 The EGR/SEAP reporter construct can be assembled by the following protocol. The EGR-1 promoter sequence (-633 to +1)(Sakamoto K et al., Oncogene 6:867-871 (1991)) can be PCR amplified from human genomic DNA using the following primers:

5' GCGCTCGAGGGATGACAGCGATAGAACCCCGG -3' (SEQ ID NO:6)

5' GCGAAGCTTCGCGACTCCCCGGATCCGCCTC-3' (SEQ ID NO:7)

15 Using the GAS:SEAP/Neo vector produced in Example 12, EGR1 amplified product can then be inserted into this vector. Linearize the GAS:SEAP/Neo vector using restriction enzymes XhoI/HindIII, removing the GAS/SV40 stuffer. Restrict the EGR1 amplified product with these same enzymes. Ligate the vector and the EGR1 promoter.

20 To prepare 96 well-plates for cell culture, two mls of a coating solution (1:30 dilution of collagen type I (Upstate Biotech Inc. Cat#08-115) in 30% ethanol (filter sterilized)) is added per one 10 cm plate or 50 ml per well of the 96-well plate, and allowed to air dry for 2 hr.

PC12 cells are routinely grown in RPMI-1640 medium (Bio Whittaker)  
25 containing 10% horse serum (JRH BIOSCIENCES, Cat. # 12449-78P), 5% heat-inactivated fetal bovine serum (FBS) supplemented with 100 units/ml penicillin and 100 ug/ml streptomycin on a precoated 10 cm tissue culture dish. One to four split is done every three to four days. Cells are removed from the plates by scraping and resuspended with pipetting up and down for more than 15 times.

30 Transfect the EGR/SEAP/Neo construct into PC12 using the Lipofectamine protocol described in Example 11. EGR-SEAP/PC12 stable cells are obtained by growing the cells in 300 ug/ml G418. The G418-free medium is used for routine growth but every one to two months, the cells should be re-grown in 300 ug/ml G418 for couple of passages.

35 To assay for neuronal activity, a 10 cm plate with cells around 70 to 80% confluent is screened by removing the old medium. Wash the cells once with PBS

(Phosphate buffered saline). Then starve the cells in low serum medium (RPMI-1640 containing 1% horse serum and 0.5% FBS with antibiotics) overnight.

5 The next morning, remove the medium and wash the cells with PBS. Scrape off the cells from the plate, suspend the cells well in 2 ml low serum medium. Count the cell number and add more low serum medium to reach final cell density as  $5 \times 10^5$  cells/ml.

Add 200  $\mu$ l of the cell suspension to each well of 96-well plate (equivalent to  $1 \times 10^5$  cells/well). Add 50  $\mu$ l supernatant produced by Example 11, 37°C for 48 to 72 hr. As a positive control, a growth factor known to activate PC12 cells through EGR can be used, such as 50 ng/ $\mu$ l of Neuronal Growth Factor (NGF). Over fifty-fold  
10 induction of SEAP is typically seen in the positive control wells. SEAP assay the supernatant according to Example 17.

#### **Example 16: High-Throughput Screening Assay for T-cell Activity**

15 NF- $\kappa$ B (Nuclear Factor  $\kappa$ B) is a transcription factor activated by a wide variety of agents including the inflammatory cytokines IL-1 and TNF, CD30 and CD40, lymphotoxin-alpha and lymphotoxin-beta, by exposure to LPS or thrombin, and by expression of certain viral gene products. As a transcription factor, NF- $\kappa$ B regulates the expression of genes involved in immune cell activation, control of apoptosis (NF-  
20  $\kappa$ B appears to shield cells from apoptosis), B and T-cell development, anti-viral and antimicrobial responses, and multiple stress responses.

In non-stimulated conditions, NF-  $\kappa$ B is retained in the cytoplasm with I- $\kappa$ B (Inhibitor  $\kappa$ B). However, upon stimulation, I-  $\kappa$ B is phosphorylated and degraded, causing NF-  $\kappa$ B to shuttle to the nucleus, thereby activating transcription of target  
25 genes. Target genes activated by NF-  $\kappa$ B include IL-2, IL-6, GM-CSF, ICAM-1 and class 1 MHC.

Due to its central role and ability to respond to a range of stimuli, reporter constructs utilizing the NF- $\kappa$ B promoter element are used to screen the supernatants produced in Example 11. Activators or inhibitors of NF- $\kappa$ B would be useful in treating  
30 diseases. For example, inhibitors of NF- $\kappa$ B could be used to treat those diseases related to the acute or chronic activation of NF- $\kappa$ B, such as rheumatoid arthritis.

To construct a vector containing the NF- $\kappa$ B promoter element, a PCR based strategy is employed. The upstream primer contains four tandem copies of the NF- $\kappa$ B binding site (GGGGACTTTCCC) (SEQ ID NO:8), 18 bp of sequence complementary to the 5' end of the SV40 early promoter sequence, and is flanked with an XhoI site:

5 5':GCGGCCTCGAGGGGACTTTCCCGGGGACTTTCCGGGGACTTTCCGGGGAC  
TTTCCATCCTGCCATCTCAATTAG:3' (SEQ ID NO:9)

The downstream primer is complementary to the 3' end of the SV40 promoter and is flanked with a Hind III site:

5':GCGGCAAGCTTTTTGCAAAGCCTAGGC:3' (SEQ ID NO:4)

10 PCR amplification is performed using the SV40 promoter template present in the pB-gal:promoter plasmid obtained from Clontech. The resulting PCR fragment is digested with XhoI and Hind III and subcloned into BLSK2-. (Stratagene) Sequencing with the T7 and T3 primers confirms the insert contains the following sequence:

15 5':CTCGAGGGGACTTTCCCGGGGACTTTCCGGGGACTTTCCGGGGACTTTCC  
ATCTGCCATCTCAATTAGTCAGCAACCATAGTCCCGCCCCTAACTCCGCCCCA  
TCCCGCCCCTAACTCCGCCCAGTTCCGCCCATTCTCCGCCCCATGGCTGACT  
AATTTTTTTTATTTATGCAGAGGCCGAGGCCGCTCGGCCTCTGAGCTATTC  
20 CAGAAGTAGTGAGGAGGCTTTTTTGGAGGCCTAGGCTTTTGCAAAAAGCTT:  
3' (SEQ ID NO:10)

Next, replace the SV40 minimal promoter element present in the pSEAP2-promoter plasmid (Clontech) with this NF- $\kappa$ B/SV40 fragment using XhoI and HindIII.

25 However, this vector does not contain a neomycin resistance gene, and therefore, is not preferred for mammalian expression systems.

In order to generate stable mammalian cell lines, the NF- $\kappa$ B/SV40/SEAP cassette is removed from the above NF- $\kappa$ B/SEAP vector using restriction enzymes SalI and NotI, and inserted into a vector containing neomycin resistance. Particularly, the

30 NF- $\kappa$ B/SV40/SEAP cassette was inserted into pGFP-1 (Clontech), replacing the GFP gene, after restricting pGFP-1 with SalI and NotI.

Once NF- $\kappa$ B/SV40/SEAP/Neo vector is created, stable Jurkat T-cells are created and maintained according to the protocol described in Example 13. Similarly, the method for assaying supernatants with these stable Jurkat T-cells is also described

in Example 13. As a positive control, exogenous TNF alpha (0.1, 1, 10 ng) is added to wells H9, H10, and H11, with a 5-10 fold activation typically observed.

#### **Example 17: Assay for SEAP Activity**

- 5 As a reporter molecule for the assays described in Examples 13-16, SEAP activity is assayed using the Tropix Phospho-light Kit (Cat. BP-400) according to the following general procedure. The Tropix Phospho-light Kit supplies the Dilution, Assay, and Reaction Buffers used below.

- 10 Prime a dispenser with the 2.5x Dilution Buffer and dispense 15 µl of 2.5x dilution buffer into Optiplates containing 35 µl of a supernatant. Seal the plates with a plastic sealer and incubate at 65°C for 30 min. Separate the Optiplates to avoid uneven heating.

- Cool the samples to room temperature for 15 minutes. Empty the dispenser and prime with the Assay Buffer. Add 50 µl Assay Buffer and incubate at room temperature 5 min. Empty the dispenser and prime with the Reaction Buffer (see the table below). Add 50 µl Reaction Buffer and incubate at room temperature for 20 minutes. Since the intensity of the chemiluminescent signal is time dependent, and it takes about 10 minutes to read 5 plates on luminometer, one should treat 5 plates at each time and start the second set 10 minutes later.

- 20 Read the relative light unit in the luminometer. Set H12 as blank, and print the results. An increase in chemiluminescence indicates reporter activity.

#### **Reaction Buffer Formulation:**

# of plates	Rxn buffer diluent (ml)	CSPD (ml)
10	60	3
11	65	3.25
12	70	3.5
13	75	3.75
14	80	4
15	85	4.25
16	90	4.5
17	95	4.75
18	100	5
19	105	5.25
20	110	5.5
21	115	5.75
22	120	6
23	125	6.25
24	130	6.5
25	135	6.75
26	140	7
27	145	7.25



28	150	7.5
29	155	7.75
30	160	8
31	165	8.25
32	170	8.5
33	175	8.75
34	180	9
35	185	9.25
36	190	9.5
37	195	9.75
38	200	10
39	205	10.25
40	210	10.5
41	215	10.75
42	220	11
43	225	11.25
44	230	11.5
45	235	11.75
46	240	12
47	245	12.25
48	250	12.5
49	255	12.75
50	260	13

**Example 18: High-Throughput Screening Assay Identifying Changes in Small Molecule Concentration and Membrane Permeability**

Binding of a ligand to a receptor is known to alter intracellular levels of small molecules, such as calcium, potassium, sodium, and pH, as well as alter membrane potential. These alterations can be measured in an assay to identify supernatants which bind to receptors of a particular cell. Although the following protocol describes an assay for calcium, this protocol can easily be modified to detect changes in potassium, sodium, pH, membrane potential, or any other small molecule which is detectable by a fluorescent probe:

The following assay uses Fluorometric Imaging Plate Reader ("FLIPR") to measure changes in fluorescent molecules (Molecular Probes) that bind small molecules. Clearly, any fluorescent molecule detecting a small molecule can be used instead of the calcium fluorescent molecule, fluo-3, used here.

For adherent cells, seed the cells at 10,000 -20,000 cells/well in a Co-star black 96-well plate with clear bottom. The plate is incubated in a CO<sub>2</sub> incubator for 20 hours. The adherent cells are washed two times in Biotek washer with 200 ul of HBSS (Hank's Balanced Salt Solution) leaving 100 ul of buffer after the final wash.

A stock solution of 1 mg/ml fluo-3 is made in 10% pluronic acid DMSO. To load the cells with fluo-3, 50 ul of 12 ug/ml fluo-3 is added to each well. The plate is

incubated at 37°C in a CO<sub>2</sub> incubator for 60 min. The plate is washed four times in the Biotek washer with HBSS leaving 100 ul of buffer.

For non-adherent cells, the cells are spun down from culture media. Cells are re-suspended to 2-5x10<sup>6</sup> cells/ml with HBSS in a 50-ml conical tube. 4 ul of 1 mg/ml fluo-3 solution in 10% pluronic acid DMSO is added to each ml of cell suspension. The tube is then placed in a 37°C water bath for 30-60 min. The cells are washed twice with HBSS, resuspended to 1x10<sup>6</sup> cells/ml, and dispensed into a microplate, 100 ul/well. The plate is centrifuged at 1000 rpm for 5 min. The plate is then washed once in Denley CellWash with 200 ul, followed by an aspiration step to 100 ul final volume.

For a non-cell based assay, each well contains a fluorescent molecule, such as fluo-3. The supernatant is added to the well, and a change in fluorescence is detected.

To measure the fluorescence of intracellular calcium, the FLIPR is set for the following parameters: (1) System gain is 300-800 mW; (2) Exposure time is 0.4 second; (3) Camera F/stop is F/2; (4) Excitation is 488 nm; (5) Emission is 530 nm; and (6) Sample addition is 50 ul. Increased emission at 530 nm indicates an extracellular signaling event which has resulted in an increase in the intracellular Ca<sup>++</sup> concentration.

#### **Example 19: High-Throughput Screening Assay Identifying Tyrosine Kinase Activity**

The Protein Tyrosine Kinases (PTK) represent a diverse group of transmembrane and cytoplasmic kinases. Within the Receptor Protein Tyrosine Kinase (RPTK) group are receptors for a range of mitogenic and metabolic growth factors including the PDGF, FGF, EGF, NGF, HGF and Insulin receptor subfamilies. In addition there are a large family of RPTKs for which the corresponding ligand is unknown. Ligands for RPTKs include mainly secreted small proteins, but also membrane-bound and extracellular matrix proteins.

Activation of RPTK by ligands involves ligand-mediated receptor dimerization, resulting in transphosphorylation of the receptor subunits and activation of the cytoplasmic tyrosine kinases. The cytoplasmic tyrosine kinases include receptor associated tyrosine kinases of the src-family (e.g., src, yes, lck, lyn, fyn) and non-receptor linked and cytosolic protein tyrosine kinases, such as the Jak family, members of which mediate signal transduction triggered by the cytokine superfamily of receptors (e.g., the Interleukins, Interferons, GM-CSF, and Leptin).

Because of the wide range of known factors capable of stimulating tyrosine kinase activity, the identification of novel human secreted proteins capable of activating

tyrosine kinase signal transduction pathways are of interest. Therefore, the following protocol is designed to identify those novel human secreted proteins capable of activating the tyrosine kinase signal transduction pathways.

Seed target cells (e.g., primary keratinocytes) at a density of approximately  
5 25,000 cells per well in a 96 well Loprodyne Silent Screen Plates purchased from  
Nalge Nunc (Naperville, IL). The plates are sterilized with two 30 minute rinses with  
100% ethanol, rinsed with water and dried overnight. Some plates are coated for 2 hr  
with 100 ml of cell culture grade type I collagen (50 mg/ml), gelatin (2%) or polylysine  
(50 mg/ml), all of which can be purchased from Sigma Chemicals (St. Louis, MO) or  
10 10% Matrigel purchased from Becton Dickinson (Bedford, MA), or calf serum, rinsed  
with PBS and stored at 4°C. Cell growth on these plates is assayed by seeding 5,000  
cells/well in growth medium and indirect quantitation of cell number through use of  
AlamarBlue as described by the manufacturer Alamar Biosciences, Inc. (Sacramento,  
CA) after 48 hr. Falcon plate covers #3071 from Becton Dickinson (Bedford, MA) are  
15 used to cover the Loprodyne Silent Screen Plates. Falcon Microtest III cell culture  
plates can also be used in some proliferation experiments.

To prepare extracts, A431 cells are seeded onto the nylon membranes of  
Loprodyne plates (20,000/200ml/well) and cultured overnight in complete medium.  
Cells are quiesced by incubation in serum-free basal medium for 24 hr. After 5-20  
20 minutes treatment with EGF (60ng/ml) or 50 ul of the supernatant produced in Example  
11, the medium was removed and 100 ml of extraction buffer ((20 mM HEPES pH  
7.5, 0.15 M NaCl, 1% Triton X-100, 0.1% SDS, 2 mM Na<sub>3</sub>VO<sub>4</sub>, 2 mM Na<sub>4</sub>P<sub>2</sub>O<sub>7</sub>  
and a cocktail of protease inhibitors (# 1836170) obtained from Boehringer Mannheim  
(Indianapolis, IN) is added to each well and the plate is shaken on a rotating shaker for  
25 5 minutes at 4°C. The plate is then placed in a vacuum transfer manifold and the extract  
filtered through the 0.45 mm membrane bottoms of each well using house vacuum.  
Extracts are collected in a 96-well catch/assay plate in the bottom of the vacuum  
manifold and immediately placed on ice. To obtain extracts clarified by centrifugation,  
the content of each well, after detergent solubilization for 5 minutes, is removed and  
30 centrifuged for 15 minutes at 4°C at 16,000 x g.

Test the filtered extracts for levels of tyrosine kinase activity. Although many  
methods of detecting tyrosine kinase activity are known, one method is described here.

Generally, the tyrosine kinase activity of a supernatant is evaluated by  
determining its ability to phosphorylate a tyrosine residue on a specific substrate (a  
35 biotinylated peptide). Biotinylated peptides that can be used for this purpose include  
PSK1 (corresponding to amino acids 6-20 of the cell division kinase cdc2-p34) and

PSK2 (corresponding to amino acids 1-17 of gastrin). Both peptides are substrates for a range of tyrosine kinases and are available from Boehringer Mannheim.

The tyrosine kinase reaction is set up by adding the following components in order. First, add 10ul of 5uM Biotinylated Peptide, then 10ul ATP/Mg<sub>2+</sub> (5mM ATP/50mM MgCl<sub>2</sub>), then 10ul of 5x Assay Buffer (40mM imidazole hydrochloride, pH7.3, 40 mM beta-glycerophosphate, 1mM EGTA, 100mM MgCl<sub>2</sub>, 5 mM MnCl<sub>2</sub>, 0.5 mg/ml BSA), then 5ul of Sodium Vanadate(1mM), and then 5ul of water. Mix the components gently and preincubate the reaction mix at 30°C for 2 min. Initiate the reaction by adding 10ul of the control enzyme or the filtered supernatant.

10 The tyrosine kinase assay reaction is then terminated by adding 10 ul of 120mM EDTA and place the reactions on ice.

Tyrosine kinase activity is determined by transferring 50 ul aliquot of reaction mixture to a microtiter plate (MTP) module and incubating at 37°C for 20 min. This allows the streptavidin coated 96 well plate to associate with the biotinylated peptide. 15 Wash the MTP module with 300ul/well of PBS four times. Next add 75 ul of anti-phosphotyrosine antibody conjugated to horse radish peroxidase(anti-P-Tyr-POD(0.5u/ml)) to each well and incubate at 37°C for one hour. Wash the well as above.

20 Next add 100ul of peroxidase substrate solution (Boehringer Mannheim) and incubate at room temperature for at least 5 mins (up to 30 min). Measure the absorbance of the sample at 405 nm by using ELISA reader. The level of bound peroxidase activity is quantitated using an ELISA reader and reflects the level of tyrosine kinase activity.

#### 25 **Example 20: High-Throughput Screening Assay Identifying Phosphorylation Activity**

As a potential alternative and/or complement to the assay of protein tyrosine kinase activity described in Example 19, an assay which detects activation (phosphorylation) of major intracellular signal transduction intermediates can also be 30 used. For example, as described below one particular assay can detect tyrosine phosphorylation of the Erk-1 and Erk-2 kinases. However, phosphorylation of other molecules, such as Raf, JNK, p38 MAP, Map kinase kinase (MEK), MEK kinase, Src, Muscle specific kinase (MuSK), IRAK, Tec, and Janus, as well as any other phosphoserine, phosphotyrosine, or phosphothreonine molecule, can be detected by 35 substituting these molecules for Erk-1 or Erk-2 in the following assay.

Specifically, assay plates are made by coating the wells of a 96-well ELISA plate with 0.1ml of protein G (1ug/ml) for 2 hr at room temp, (RT). The plates are then rinsed with PBS and blocked with 3% BSA/PBS for 1 hr at RT. The protein G plates are then treated with 2 commercial monoclonal antibodies (100ng/well) against Erk-1 and Erk-2 (1 hr at RT) (Santa Cruz Biotechnology). (To detect other molecules, this step can easily be modified by substituting a monoclonal antibody detecting any of the above described molecules.) After 3-5 rinses with PBS, the plates are stored at 4°C until use.

A431 cells are seeded at 20,000/well in a 96-well Loprodyne filterplate and cultured overnight in growth medium. The cells are then starved for 48 hr in basal medium (DMEM) and then treated with EGF (6ng/well) or 50 ul of the supernatants obtained in Example 11 for 5-20 minutes. The cells are then solubilized and extracts filtered directly into the assay plate.

After incubation with the extract for 1 hr at RT, the wells are again rinsed. As a positive control, a commercial preparation of MAP kinase (10ng/well) is used in place of A431 extract. Plates are then treated with a commercial polyclonal (rabbit) antibody (1ug/ml) which specifically recognizes the phosphorylated epitope of the Erk-1 and Erk-2 kinases (1 hr at RT). This antibody is biotinylated by standard procedures. The bound polyclonal antibody is then quantitated by successive incubations with Europium-streptavidin and Europium fluorescence enhancing reagent in the Wallac DELFIA instrument (time-resolved fluorescence). An increased fluorescent signal over background indicates a phosphorylation.

**Example 21: Method of Determining Alterations in a Gene**  
**Corresponding to a Polynucleotide**

RNA isolated from entire families or individual patients presenting with a phenotype of interest (such as a disease) is be isolated. cDNA is then generated from these RNA samples using protocols known in the art. (See, Sambrook.) The cDNA is then used as a template for PCR, employing primers surrounding regions of interest in SEQ ID NO:X. Suggested PCR conditions consist of 35 cycles at 95°C for 30 seconds; 60-120 seconds at 52-58°C; and 60-120 seconds at 70°C, using buffer solutions described in Sidransky, D., et al., Science 252:706 (1991).

PCR products are then sequenced using primers labeled at their 5' end with T4 polynucleotide kinase, employing SequiTherm Polymerase. (Epicentre Technologies).

The intron-exon borders of selected exons is also determined and genomic PCR

products analyzed to confirm the results. PCR products harboring suspected mutations is then cloned and sequenced to validate the results of the direct sequencing.

5 PCR products is cloned into T-tailed vectors as described in Holton, T.A. and Graham, M.W., *Nucleic Acids Research*, 19:1156 (1991) and sequenced with T7 polymerase (United States Biochemical). Affected individuals are identified by mutations not present in unaffected individuals.

10 Genomic rearrangements are also observed as a method of determining alterations in a gene corresponding to a polynucleotide. Genomic clones isolated according to Example 2 are nick-translated with digoxigenin deoxy-uridine 5'-triphosphate (Boehringer Mannheim), and FISH performed as described in Johnson, Cg. et al., *Methods Cell Biol.* 35:73-99 (1991). Hybridization with the labeled probe is carried out using a vast excess of human cot-1 DNA for specific hybridization to the corresponding genomic locus.

15 Chromosomes are counterstained with 4,6-diamino-2-phenylidole and propidium iodide, producing a combination of C- and R-bands. Aligned images for precise mapping are obtained using a triple-band filter set (Chroma Technology, Brattleboro, VT) in combination with a cooled charge-coupled device camera (Photometrics, Tucson, AZ) and variable excitation wavelength filters. (Johnson, Cv. et al., *Genet. Anal. Tech. Appl.*, 8:75 (1991).) Image collection, analysis and  
20 chromosomal fractional length measurements are performed using the ISee Graphical Program System. (Inovision Corporation, Durham, NC.) Chromosome alterations of the genomic region hybridized by the probe are identified as insertions, deletions, and translocations. These alterations are used as a diagnostic marker for an associated disease.

25

**Example 22: Method of Detecting Abnormal Levels of a Polypeptide in a Biological Sample**

A polypeptide of the present invention can be detected in a biological sample, and if an increased or decreased level of the polypeptide is detected, this polypeptide is  
30 a marker for a particular phenotype. Methods of detection are numerous, and thus, it is understood that one skilled in the art can modify the following assay to fit their particular needs.

For example, antibody-sandwich ELISAs are used to detect polypeptides in a sample, preferably a biological sample. Wells of a microtiter plate are coated with  
35 specific antibodies, at a final concentration of 0.2 to 10 ug/ml. The antibodies are either monoclonal or polyclonal and are produced by the method described in Example 10.

The wells are blocked so that non-specific binding of the polypeptide to the well is reduced.

The coated wells are then incubated for > 2 hours at RT with a sample containing the polypeptide. Preferably, serial dilutions of the sample should be used to validate results. The plates are then washed three times with deionized or distilled water to remove unbounded polypeptide.

Next, 50 ul of specific antibody-alkaline phosphatase conjugate, at a concentration of 25-400 ng, is added and incubated for 2 hours at room temperature. The plates are again washed three times with deionized or distilled water to remove unbounded conjugate.

Add 75 ul of 4-methylumbelliferyl phosphate (MUP) or p-nitrophenyl phosphate (NPP) substrate solution to each well and incubate 1 hour at room temperature. Measure the reaction by a microtiter plate reader. Prepare a standard curve, using serial dilutions of a control sample, and plot polypeptide concentration on the X-axis (log scale) and fluorescence or absorbance of the Y-axis (linear scale). Interpolate the concentration of the polypeptide in the sample using the standard curve.

#### **Example 23: Formulating a Polypeptide**

The secreted polypeptide composition will be formulated and dosed in a fashion consistent with good medical practice, taking into account the clinical condition of the individual patient (especially the side effects of treatment with the secreted polypeptide alone), the site of delivery, the method of administration, the scheduling of administration, and other factors known to practitioners. The "effective amount" for purposes herein is thus determined by such considerations.

As a general proposition, the total pharmaceutically effective amount of secreted polypeptide administered parenterally per dose will be in the range of about 1  $\mu\text{g/kg/day}$  to 10  $\text{mg/kg/day}$  of patient body weight, although, as noted above, this will be subject to therapeutic discretion. More preferably, this dose is at least 0.01  $\text{mg/kg/day}$ , and most preferably for humans between about 0.01 and 1  $\text{mg/kg/day}$  for the hormone. If given continuously, the secreted polypeptide is typically administered at a dose rate of about 1  $\mu\text{g/kg/hour}$  to about 50  $\mu\text{g/kg/hour}$ , either by 1-4 injections per day or by continuous subcutaneous infusions, for example, using a mini-pump. An intravenous bag solution may also be employed. The length of treatment needed to observe changes and the interval following treatment for responses to occur appears to vary depending on the desired effect.

Pharmaceutical compositions containing the secreted protein of the invention are administered orally, rectally, parenterally, intracisternally, intravaginally,

intraperitoneally, topically (as by powders, ointments, gels, drops or transdermal patch), buccally, or as an oral or nasal spray. "Pharmaceutically acceptable carrier" refers to a non-toxic solid, semisolid or liquid filler, diluent, encapsulating material or formulation auxiliary of any type. The term "parenteral" as used herein refers to modes  
5 of administration which include intravenous, intramuscular, intraperitoneal, intrasternal, subcutaneous and intraarticular injection and infusion.

The secreted polypeptide is also suitably administered by sustained-release systems. Suitable examples of sustained-release compositions include semi-permeable polymer matrices in the form of shaped articles, e.g., films, or microcapsules.  
10 Sustained-release matrices include polylactides (U.S. Pat. No. 3,773,919, EP 58,481), copolymers of L-glutamic acid and gamma-ethyl-L-glutamate (Sidman, U. et al., Biopolymers 22:547-556 (1983)), poly (2- hydroxyethyl methacrylate) (R. Langer et al., J. Biomed. Mater. Res. 15:167-277 (1981), and R. Langer, Chem. Tech. 12:98-105 (1982)), ethylene vinyl acetate (R. Langer et al.) or poly-D- (-)-3-hydroxybutyric  
15 acid (EP 133,988). Sustained-release compositions also include liposomally entrapped polypeptides. Liposomes containing the secreted polypeptide are prepared by methods known per se: DE 3,218,121; Epstein et al., Proc. Natl. Acad. Sci. USA 82:3688-3692 (1985); Hwang et al., Proc. Natl. Acad. Sci. USA 77:4030-4034 (1980); EP 52,322; EP 36,676; EP 88,046; EP 143,949; EP 142,641; Japanese Pat. Appl. 83-118008;  
20 U.S. Pat. Nos. 4,485,045 and 4,544,545; and EP 102,324. Ordinarily, the liposomes are of the small (about 200-800 Angstroms) unilamellar type in which the lipid content is greater than about 30 mol. percent cholesterol, the selected proportion being adjusted for the optimal secreted polypeptide therapy.

For parenteral administration, in one embodiment, the secreted polypeptide is  
25 formulated generally by mixing it at the desired degree of purity, in a unit dosage injectable form (solution, suspension, or emulsion), with a pharmaceutically acceptable carrier, i.e., one that is non-toxic to recipients at the dosages and concentrations employed and is compatible with other ingredients of the formulation. For example, the formulation preferably does not include oxidizing agents and other compounds that are  
30 known to be deleterious to polypeptides.

Generally, the formulations are prepared by contacting the polypeptide uniformly and intimately with liquid carriers or finely divided solid carriers or both. Then, if necessary, the product is shaped into the desired formulation. Preferably the carrier is a parenteral carrier, more preferably a solution that is isotonic with the blood  
35 of the recipient. Examples of such carrier vehicles include water, saline, Ringer's solution, and dextrose solution. Non-aqueous vehicles such as fixed oils and ethyl oleate are also useful herein, as well as liposomes.



The carrier suitably contains minor amounts of additives such as substances that enhance isotonicity and chemical stability. Such materials are non-toxic to recipients at the dosages and concentrations employed, and include buffers such as phosphate, citrate, succinate, acetic acid, and other organic acids or their salts; antioxidants such as ascorbic acid; low molecular weight (less than about ten residues) polypeptides, e.g., polyarginine or tripeptides; proteins, such as serum albumin, gelatin, or immunoglobulins; hydrophilic polymers such as polyvinylpyrrolidone; amino acids, such as glycine, glutamic acid, aspartic acid, or arginine; monosaccharides, disaccharides, and other carbohydrates including cellulose or its derivatives, glucose, manose, or dextrans; chelating agents such as EDTA; sugar alcohols such as mannitol or sorbitol; counterions such as sodium; and/or nonionic surfactants such as polysorbates, poloxamers, or PEG.

The secreted polypeptide is typically formulated in such vehicles at a concentration of about 0.1 mg/ml to 100 mg/ml, preferably 1-10 mg/ml, at a pH of about 3 to 8. It will be understood that the use of certain of the foregoing excipients, carriers, or stabilizers will result in the formation of polypeptide salts.

Any polypeptide to be used for therapeutic administration can be sterile. Sterility is readily accomplished by filtration through sterile filtration membranes (e.g., 0.2 micron membranes). Therapeutic polypeptide compositions generally are placed into a container having a sterile access port, for example, an intravenous solution bag or vial having a stopper pierceable by a hypodermic injection needle.

Polypeptides ordinarily will be stored in unit or multi-dose containers, for example, sealed ampoules or vials, as an aqueous solution or as a lyophilized formulation for reconstitution. As an example of a lyophilized formulation, 10-ml vials are filled with 5 ml of sterile-filtered 1% (w/v) aqueous polypeptide solution, and the resulting mixture is lyophilized. The infusion solution is prepared by reconstituting the lyophilized polypeptide using bacteriostatic Water-for-Injection.

The invention also provides a pharmaceutical pack or kit comprising one or more containers filled with one or more of the ingredients of the pharmaceutical compositions of the invention. Associated with such container(s) can be a notice in the form prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceuticals or biological products, which notice reflects approval by the agency of manufacture, use or sale for human administration. In addition, the polypeptides of the present invention may be employed in conjunction with other therapeutic compounds.

#### **Example 24: Method of Treating Decreased Levels of the Polypeptide**

It will be appreciated that conditions caused by a decrease in the standard or normal expression level of a secreted protein in an individual can be treated by administering the polypeptide of the present invention, preferably in the secreted form. Thus, the invention also provides a method of treatment of an individual in need of an increased level of the polypeptide comprising administering to such an individual a pharmaceutical composition comprising an amount of the polypeptide to increase the activity level of the polypeptide in such an individual.

For example, a patient with decreased levels of a polypeptide receives a daily dose 0.1-100 ug/kg of the polypeptide for six consecutive days. Preferably, the polypeptide is in the secreted form. The exact details of the dosing scheme, based on administration and formulation, are provided in Example 23.

#### **Example 25: Method of Treating Increased Levels of the Polypeptide**

Antisense technology is used to inhibit production of a polypeptide of the present invention. This technology is one example of a method of decreasing levels of a polypeptide, preferably a secreted form, due to a variety of etiologies, such as cancer.

For example, a patient diagnosed with abnormally increased levels of a polypeptide is administered intravenously antisense polynucleotides at 0.5, 1.0, 1.5, 2.0 and 3.0 mg/kg day for 21 days. This treatment is repeated after a 7-day rest period if the treatment was well tolerated. The formulation of the antisense polynucleotide is provided in Example 23.

#### **Example 26: Method of Treatment Using Gene Therapy**

One method of gene therapy transplants fibroblasts, which are capable of expressing a polypeptide, onto a patient. Generally, fibroblasts are obtained from a subject by skin biopsy. The resulting tissue is placed in tissue-culture medium and separated into small pieces. Small chunks of the tissue are placed on a wet surface of a tissue culture flask, approximately ten pieces are placed in each flask. The flask is turned upside down, closed tight and left at room temperature over night. After 24 hours at room temperature, the flask is inverted and the chunks of tissue remain fixed to the bottom of the flask and fresh media (e.g., Ham's F12 media, with 10% FBS, penicillin and streptomycin) is added. The flasks are then incubated at 37°C for approximately one week.

At this time, fresh media is added and subsequently changed every several days. After an additional two weeks in culture, a monolayer of fibroblasts emerge. The monolayer is trypsinized and scaled into larger flasks.

pMV-7 (Kirschmeier, P.T. et al., DNA, 7:219-25 (1988)), flanked by the long terminal repeats of the Moloney murine sarcoma virus, is digested with EcoRI and HindIII and subsequently treated with calf intestinal phosphatase. The linear vector is fractionated on agarose gel and purified, using glass beads.

5 The cDNA encoding a polypeptide of the present invention can be amplified using PCR primers which correspond to the 5' and 3' end sequences respectively as set forth in Example 1. Preferably, the 5' primer contains an EcoRI site and the 3' primer includes a HindIII site. Equal quantities of the Moloney murine sarcoma virus linear backbone and the amplified EcoRI and HindIII fragment are added together, in the  
10 presence of T4 DNA ligase. The resulting mixture is maintained under conditions appropriate for ligation of the two fragments. The ligation mixture is then used to transform bacteria HB101, which are then plated onto agar containing kanamycin for the purpose of confirming that the vector has the gene of interest properly inserted.

The amphotropic pA317 or GP+am12 packaging cells are grown in tissue  
15 culture to confluent density in Dulbecco's Modified Eagles Medium (DMEM) with 10% calf serum (CS), penicillin and streptomycin. The MSV vector containing the gene is then added to the media and the packaging cells transduced with the vector. The packaging cells now produce infectious viral particles containing the gene (the packaging cells are now referred to as producer cells).

20 Fresh media is added to the transduced producer cells, and subsequently, the media is harvested from a 10 cm plate of confluent producer cells. The spent media, containing the infectious viral particles, is filtered through a millipore filter to remove detached producer cells and this media is then used to infect fibroblast cells. Media is removed from a sub-confluent plate of fibroblasts and quickly replaced with the media  
25 from the producer cells. This media is removed and replaced with fresh media. If the titer of virus is high, then virtually all fibroblasts will be infected and no selection is required. If the titer is very low, then it is necessary to use a retroviral vector that has a selectable marker, such as neo or his. Once the fibroblasts have been efficiently infected, the fibroblasts are analyzed to determine whether protein is produced.

30 The engineered fibroblasts are then transplanted onto the host, either alone or after having been grown to confluence on cytodex 3 microcarrier beads.

#### **Example 27: Method of Treatment Using Gene Therapy - In Vivo**

35 Another aspect of the present invention is using *in vivo* gene therapy methods to treat disorders, diseases and conditions. The gene therapy method relates to the introduction of naked nucleic acid (DNA, RNA, and antisense DNA or RNA) sequences into an animal to increase or decrease the expression

of the polypeptide of the present invention. A polynucleotide of the present invention may be operatively linked to a promoter or any other genetic elements necessary for the expression of the encoded polypeptide by the target tissue. Such gene therapy and delivery techniques and methods are known in the art, see, for example, WO90/11092, WO98/11779; U.S. Patent NO. 5693622, 5705151, 5580859; Tabata H. et al. (1997) *Cardiovasc. Res.* 35(3):470-479, Chao J et al. (1997) *Pharmacol. Res.* 35(6):517-522, Wolff J.A. (1997) *Neuromuscul. Disord.* 7(5):314-318, Schwartz B. et al. (1996) *Gene Ther.* 3(5):405-411, Tsurumi Y. et al. (1996) *Circulation* 94(12):3281-3290 (incorporated herein by reference).

The polynucleotide constructs of the present invention may be delivered by any method that delivers injectable materials to the cells of an animal, such as, injection into the interstitial space of tissues (heart, muscle, skin, lung, liver, intestine and the like). These polynucleotide constructs can be delivered in a pharmaceutically acceptable liquid or aqueous carrier.

The term "naked" polynucleotide, DNA or RNA, refers to sequences that are free from any delivery vehicle that acts to assist, promote, or facilitate entry into the cell, including viral sequences, viral particles, liposome formulations, lipofectin or precipitating agents and the like. However, the polynucleotides may also be delivered in liposome formulations (such as those taught in Felgner P.L. et al. (1995) *Ann. NY Acad. Sci.* 772:126-139 and Abdallah B. et al. (1995) *Biol. Cell* 85(1):1-7) which can be prepared by methods well known to those skilled in the art.

The polynucleotide vector constructs of the present invention used in the gene therapy method are preferably constructs that will not integrate into the host genome nor will they contain sequences that allow for replication. Any strong promoter known to those skilled in the art can be used for driving the expression of DNA. Unlike other gene therapies techniques, one major advantage of introducing naked nucleic acid sequences into target cells is the transitory nature of the polynucleotide synthesis in the cells. Studies have shown that non-replicating DNA sequences can be introduced into cells to provide production of the desired polypeptide for periods of up to six months.

The polynucleotide construct of the present invention can be delivered to the interstitial space of tissues within the an animal, including of muscle, skin, brain, lung, liver, spleen, bone marrow, thymus, heart, lymph, blood, bone, cartilage, pancreas, kidney, gall bladder, stomach, intestine, testis, ovary, uterus, rectum, nervous system, eye, gland, and connective tissue. Interstitial

space of the tissues comprises the intercellular fluid, mucopolysaccharide matrix among the reticular fibers of organ tissues, elastic fibers in the walls of vessels or chambers, collagen fibers of fibrous tissues, or that same matrix within connective tissue ensheathing muscle cells or in the lacunae of bone. It is similarly the space occupied by the plasma of the circulation and the lymph fluid of the lymphatic channels. Delivery to the interstitial space of muscle tissue is preferred for the reasons discussed below. They may be conveniently delivered by injection into the tissues comprising these cells. They are preferably delivered to and expressed in persistent, non-dividing cells which are differentiated, although delivery and expression may be achieved in non-differentiated or less completely differentiated cells, such as, for example, stem cells of blood or skin fibroblasts. *In vivo* muscle cells are particularly competent in their ability to take up and express polynucleotides.

For the naked polynucleotide injection, an effective dosage amount of DNA or RNA will be in the range of from about 0.05 g/kg body weight to about 50 mg/kg body weight. Preferably the dosage will be from about 0.005 mg/kg to about 20 mg/kg and more preferably from about 0.05 mg/kg to about 5 mg/kg. Of course, as the artisan of ordinary skill will appreciate, this dosage will vary according to the tissue site of injection. The appropriate and effective dosage of nucleic acid sequence can readily be determined by those of ordinary skill in the art and may depend on the condition being treated and the route of administration. The preferred route of administration is by the parenteral route of injection into the interstitial space of tissues. However, other parenteral routes may also be used, such as, inhalation of an aerosol formulation particularly for delivery to lungs or bronchial tissues, throat or mucous membranes of the nose. In addition, naked polynucleotide constructs can be delivered to arteries during angioplasty by the catheter used in the procedure.

The dose response effects of injected polynucleotide in muscle *in vivo* is determined as follows. Suitable template DNA for production of mRNA coding for the polypeptide of the present invention is prepared in accordance with a standard recombinant DNA methodology. The template DNA, which may be either circular or linear, is either used as naked DNA or complexed with liposomes. The quadriceps muscles of mice are then injected with various amounts of the template DNA.

Five to six week old female and male Balb/C mice are anesthetized by intraperitoneal injection with 0.3 ml of 2.5% Avertin. A 1.5 cm incision is made on the anterior thigh, and the quadriceps muscle is directly visualized. The

template DNA is injected in 0.1 ml of carrier in a 1 cc syringe through a 27 gauge needle over one minute, approximately 0.5 cm from the distal insertion site of the muscle into the knee and about 0.2 cm deep. A suture is placed over the injection site for future localization, and the skin is closed with stainless steel clips.

After an appropriate incubation time (e.g., 7 days) muscle extracts are prepared by excising the entire quadriceps. Every fifth 15 um cross-section of the individual quadriceps muscles is histochemically stained for protein expression. A time course for protein expression may be done in a similar fashion except that quadriceps from different mice are harvested at different times. Persistence of DNA in muscle following injection may be determined by Southern blot analysis after preparing total cellular DNA and HIRT supernatants from injected and control mice. The results of the above experimentation in mice can be use to extrapolate proper dosages and other treatment parameters in humans and other animals using naked DNA of the present invention.

It will be clear that the invention may be practiced otherwise than as particularly described in the foregoing description and examples. Numerous modifications and variations of the present invention are possible in light of the above teachings and, therefore, are within the scope of the appended claims.

The entire disclosure of each document cited (including patents, patent applications, journal articles, abstracts, laboratory manuals, books, or other disclosures) in the Background of the Invention, Detailed Description, and Examples is hereby incorporated herein by reference.

Further, the Sequence Listing submitted herewith in paper and computer readable forms are herein incorporated by reference in their entireties.

## INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13bis)

A. The indications made below relate to the microorganism referred to in the description on page <u>79</u> , line <u>N/A</u>	
<b>B. IDENTIFICATION OF DEPOSIT</b> Further deposits are identified on an additional sheet <input type="checkbox"/>	
Name of depositary institution <div style="text-align: center;">American Type Culture Collection</div>	
Address of depositary institution (including postal code and country) 10801 University Boulevard Manassas, Virginia 20110-2209 United States of America	
Date of deposit     July 3, 1997	Accession Number     209138
<b>C. ADDITIONAL INDICATIONS</b> (leave blank if not applicable) This information is continued on an additional sheet <input type="checkbox"/>	
<b>D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE</b> (if the indications are not for all designated States)	
<b>E. SEPARATE FURNISHING OF INDICATIONS</b> (leave blank if not applicable)	
The indications listed below will be submitted to the International Bureau later (specify the general nature of the indications, e.g., "Accession Number of Deposit")	
<div style="text-align: center;">For receiving Office use only</div> <div style="border: 1px solid black; padding: 5px; margin-top: 5px;"><input checked="checked" type="checkbox"/> This sheet was received with the international application</div> <div style="border: 1px solid black; padding: 5px; margin-top: 5px;">Authorized officer <div style="text-align: center; font-family: cursive; font-size: 1.2em;">Virginia L. Lely</div></div>	<div style="text-align: center;">For International Bureau use only</div> <div style="border: 1px solid black; padding: 5px; margin-top: 5px;"><input type="checkbox"/> This sheet was received by the International Bureau on:</div> <div style="border: 1px solid black; padding: 5px; margin-top: 5px;">Authorized officer</div>

## INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13bis)

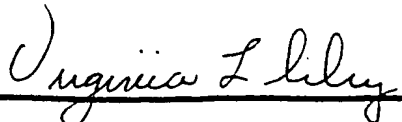
<b>A.</b> The indications made below relate to the microorganism referred to in the description on page <u>80</u> , line <u>N/A</u>	
<b>B. IDENTIFICATION OF DEPOSIT</b> <span style="float: right;">Further deposits are identified on an additional sheet <input type="checkbox"/></span>	
Name of depositary institution <div style="text-align: center;">American Type Culture Collection</div>	
Address of depositary institution (including postal code and country) 10801 University Boulevard Manassas, Virginia 20110-2209 United States of America	
Date of deposit     July 3, 1997	Accession Number     209139
<b>C. ADDITIONAL INDICATIONS</b> (leave blank if not applicable) <span style="float: right;">This information is continued on an additional sheet <input type="checkbox"/></span>	
<b>D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE</b> (if the indications are not for all designated States)	
<b>E. SEPARATE FURNISHING OF INDICATIONS</b> (leave blank if not applicable)	
The indications listed below will be submitted to the International Bureau later (specify the general nature of the indications, e.g., "Accession Number of Deposit")	

For receiving Office use only



This sheet was received with the international application

Authorized officer



For International Bureau use only



This sheet was received by the International Bureau on:


Authorized officer



## INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13bis)

A. The indications made below relate to the microorganism referred to in the description on page <u>82</u> , line <u>N/A</u>	
<b>B. IDENTIFICATION OF DEPOSIT</b> <span style="float: right;">Further deposits are identified on an additional sheet <u>---</u></span>	
Name of depositary institution: <div style="text-align: center; margin-top: 10px;">American Type Culture Collection</div>	
Address of depositary institution (including postal code and country) 10801 University Boulevard Manassas, Virginia 20110-2209 United States of America	
Date of deposit <u>July 9, 1997</u>	Accession Number <u>209141</u>
<b>C. ADDITIONAL INDICATIONS</b> (leave blank if not applicable) <span style="float: right;">This information is continued on an additional sheet <u>---</u></span>	
<b>D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE</b> (if the indications are not for all designated States)	
<b>E. SEPARATE FURNISHING OF INDICATIONS</b> (leave blank if not applicable)	
The indications listed below will be submitted to the International Bureau later (specify the general nature of the indications, e.g., "Accession Number of Deposit")	

For receiving Office use only	
<input checked="checked" type="checkbox"/> This sheet was received with the international application	
Authorized officer <div style="text-align: center; margin-top: 20px;"></div>	

For International Bureau use only	
<input type="checkbox"/> This sheet was received by the International Bureau on:	
Authorized officer	

*What Is Claimed Is:*

1. An isolated nucleic acid molecule comprising a polynucleotide having a nucleotide sequence at least 95% identical to a sequence selected from the group consisting of:
  - (a) a polynucleotide fragment of SEQ ID NO:X or a polynucleotide fragment of the cDNA sequence included in ATCC Deposit No:Z, which is hybridizable to SEQ ID NO:X;
  - (b) a polynucleotide encoding a polypeptide fragment of SEQ ID NO:Y or a polypeptide fragment encoded by the cDNA sequence included in ATCC Deposit No:Z, which is hybridizable to SEQ ID NO:X;
  - (c) a polynucleotide encoding a polypeptide domain of SEQ ID NO:Y or a polypeptide domain encoded by the cDNA sequence included in ATCC Deposit No:Z, which is hybridizable to SEQ ID NO:X;
  - (d) a polynucleotide encoding a polypeptide epitope of SEQ ID NO:Y or a polypeptide epitope encoded by the cDNA sequence included in ATCC Deposit No:Z, which is hybridizable to SEQ ID NO:X;
  - (e) a polynucleotide encoding a polypeptide of SEQ ID NO:Y or the cDNA sequence included in ATCC Deposit No:Z, which is hybridizable to SEQ ID NO:X, having biological activity;
  - (f) a polynucleotide which is a variant of SEQ ID NO:X;
  - (g) a polynucleotide which is an allelic variant of SEQ ID NO:X;
  - (h) a polynucleotide which encodes a species homologue of the SEQ ID NO:Y;
  - (i) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(h), wherein said polynucleotide does not hybridize under stringent conditions to a nucleic acid molecule having a nucleotide sequence of only A residues or of only T residues.
2. The isolated nucleic acid molecule of claim 1, wherein the polynucleotide fragment comprises a nucleotide sequence encoding a secreted protein.
3. The isolated nucleic acid molecule of claim 1, wherein the polynucleotide fragment comprises a nucleotide sequence encoding the sequence identified as SEQ ID NO:Y or the polypeptide encoded by the cDNA sequence included in ATCC Deposit No:Z, which is hybridizable to SEQ ID NO:X.

4. The isolated nucleic acid molecule of claim 1, wherein the polynucleotide fragment comprises the entire nucleotide sequence of SEQ ID NO:X or the cDNA sequence included in ATCC Deposit No:Z, which is hybridizable to SEQ ID NO:X.

5

5. The isolated nucleic acid molecule of claim 2, wherein the nucleotide sequence comprises sequential nucleotide deletions from either the C-terminus or the N-terminus.

10

6. The isolated nucleic acid molecule of claim 3, wherein the nucleotide sequence comprises sequential nucleotide deletions from either the C-terminus or the N-terminus.

15

7. A recombinant vector comprising the isolated nucleic acid molecule of claim 1.

8. A method of making a recombinant host cell comprising the isolated nucleic acid molecule of claim 1.

20

9. A recombinant host cell produced by the method of claim 8.

10. The recombinant host cell of claim 9 comprising vector sequences.

11. An isolated polypeptide comprising an amino acid sequence at least 95% identical to a sequence selected from the group consisting of:

(a) a polypeptide fragment of SEQ ID NO:Y or the encoded sequence included in ATCC Deposit No:Z;

(b) a polypeptide fragment of SEQ ID NO:Y or the encoded sequence included in ATCC Deposit No:Z, having biological activity;

(c) a polypeptide domain of SEQ ID NO:Y or the encoded sequence included in ATCC Deposit No:Z;

(d) a polypeptide epitope of SEQ ID NO:Y or the encoded sequence included in ATCC Deposit No:Z;

(e) a secreted form of SEQ ID NO:Y or the encoded sequence included in ATCC Deposit No:Z;

(f) a full length protein of SEQ ID NO:Y or the encoded sequence included in ATCC Deposit No:Z;

- (g) a variant of SEQ ID NO:Y;
- (h) an allelic variant of SEQ ID NO:Y; or
- (i) a species homologue of the SEQ ID NO:Y.

5 12. The isolated polypeptide of claim 11, wherein the secreted form or the full length protein comprises sequential amino acid deletions from either the C-terminus or the N-terminus.

10 13. An isolated antibody that binds specifically to the isolated polypeptide of claim 11.

14. A recombinant host cell that expresses the isolated polypeptide of claim 11.

15 15. A method of making an isolated polypeptide comprising:  
(a) culturing the recombinant host cell of claim 14 under conditions such that said polypeptide is expressed; and  
(b) recovering said polypeptide.

20 16. The polypeptide produced by claim 15.

17. A method for preventing, treating, or ameliorating a medical condition, comprising administering to a mammalian subject a therapeutically effective amount of the polypeptide of claim 11 or the polynucleotide of claim 1.

25 18. A method of diagnosing a pathological condition or a susceptibility to a pathological condition in a subject comprising:

(a) determining the presence or absence of a mutation in the polynucleotide of claim 1; and  
(b) diagnosing a pathological condition or a susceptibility to a pathological  
30 condition based on the presence or absence of said mutation.

19. A method of diagnosing a pathological condition or a susceptibility to a pathological condition in a subject comprising:

(a) determining the presence or amount of expression of the polypeptide of  
35 claim 11 in a biological sample; and  
(b) diagnosing a pathological condition or a susceptibility to a pathological condition based on the presence or amount of expression of the polypeptide.

20. A method for identifying a binding partner to the polypeptide of claim 11 comprising:

- 5 (a) contacting the polypeptide of claim 11 with a binding partner; and  
(b) determining whether the binding partner effects an activity of the polypeptide.

21. The gene corresponding to the cDNA sequence of SEQ ID NO:Y.

10 22. A method of identifying an activity in a biological assay, wherein the method comprises:

- (a) expressing SEQ ID NO:X in a cell;  
(b) isolating the supernatant;  
(c) detecting an activity in a biological assay; and  
15 (d) identifying the protein in the supernatant having the activity.

23. The product produced by the method of claim 22.



<110> Human Genome Sciences, Inc.

<120> 64 Human Secreted Proteins

5 <130> PZ011PCT

<140> Unassigned

<141> 1998-07-15

10 <150> 60/052,870

<151> 1997-07-16

<150> 60/052,871

15 <151> 1997-07-16

<150> 60/052,872

<151> 1997-07-16

20 <150> 60/052,661

<151> 1997-07-16

<150> 60/052,874

<151> 1997-07-16

25 <150> 60/052,873

<151> 1997-07-16

<150> 60/052,875

30 <151> 1997-07-16

<150> 60/053,440

<151> 1997-07-22

35 <150> 60/053,441

<151> 1997-07-22

<150> 60/053,442

<151> 1997-07-22

40 <150> 60/055,952

<151> 1997-08-18

<150> 60/055,725

45 <151> 1997-08-18

<150> 60/056,359

<151> 1997-08-18

50 <150> 60/055,985

<151> 1997-08-18

<150> 60/055,724

<151> 1997-08-18

55

<150> 60/055,726  
<151> 1997-08-18

5 <150> 60/056,361  
<151> 1997-08-18

<150> 60/055,989  
<151> 1997-08-18

10 <150> 60/055,946  
<151> 1997-08-18

<150> 60/055,683  
<151> 1997-08-18

15 <160> 178

<170> PatentIn Ver. 2.0

20 <210> 1  
<211> 733  
<212> DNA  
<213> Homo sapiens

25 <400> 1  
gggatccgga gcccaaatct tctgacaaaa ctcacacatg cccaccgtgc ccagcacctg 60  
aattcgaggg tgcaccgtca gtcttcctct tcccccaaa acccaaggac accctcatga 120  
tctcccggac tcttgaggtc acatgcgtgg tggaggacgt aagccacgaa gacctgagg 180  
30 tcaagttcaa ctggtacgtg gacggcgtgg aggtgcataa tgccaagaca aagccgcggg 240  
aggagcagta caacagcacg taccgtgtgg tcagcgtcct caccgtcctg caccaggact 300  
ggctgaatgg caaggagtac aagtgcagg tctccaacaa agccctccca acccccatcg 360  
agaaaaaccat ctccaaagcc aaagggcagc cccgagaacc acaggtgtac accctgcccc 420  
catcccggga tgagctgacc aagaaccagg tcagcctgac ctgcctggtc aaaggcttct 480  
35 atccaagcga catcgccgtg gagtgggaga gcaatgggca gccggagAAC aactacaaga 540  
ccacgcctcc cgtgctggac tccgacggct ccttcttctc ctacagcaag ctcaccgtgg 600  
acaagagcag gtggcagcag gggaacgtct tctcatgctc cgtgatgcat gaggctctgc 660  
acaaccacta cagcagaag agcctctccc tgtctccggg taaatgagtg cgacggccgc 720  
gactctagag gat 733

40 <210> 2  
<211> 5  
<212> PRT

45 <213> Homo sapiens

<220>  
<221> Site  
<222> (3)

50 <223> Xaa equals any one of the twenty naturally occurring L-amino acids

<400> 2  
Trp Ser Xaa Trp Ser  
1 5

55 <210> 3  
<211> 86  
<212> DNA



<213> Homo sapiens

<400> 3  
5 gcgcctcgag atttccccga aatctagatt tccccgaaat gatttccccg aaatgatttc 60  
cccgaaatat ctgccatctc aattag 86

<210> 4  
10 <211> 27  
<212> DNA  
<213> Homo sapiens

<400> 4  
15 gcggcaagct ttttgcaaag cctagggc 27

<210> 5  
20 <211> 271  
<212> DNA  
<213> Homo sapiens

<400> 5  
25 ctcgagattt ccccgaaatc tagatttccc cgaaatgatt tccccgaaat gatttccccg 60  
aaatatctgc catctcaatt agtcagcaac catagtcccc cccctaactc cgcccatccc 120  
gccccctaact ccgcccagtt ccgcccattc tccgcccatt ggctgactaa ttttttttat 180  
ttatgcagag gccgaggccg cctcggcctc tgagctattc cagaagtagt gaggaggctt 240  
ttttggaggc ctaggctttt gcaaaaagct t 271

<210> 6  
30 <211> 32  
<212> DNA  
<213> Homo sapiens

<400> 6  
35 gcgctcgagg gatgacagcg atagaacccc gg 32

<210> 7  
40 <211> 31  
<212> DNA  
<213> Homo sapiens

<400> 7  
45 gcgaagcttc gcgactcccc ggatccgcct c 31

<210> 8  
50 <211> 12  
<212> DNA  
<213> Homo sapiens

<400> 8  
55 ggggactttc cc 12

<210> 9  
60 <211> 73  
<212> DNA  
<213> Homo sapiens

5	<400> 9	gcggcctcga ggggactttc ccggggactt tccggggact ttccgggact ttccatcctg	60
		ccatctcaat tag	73
10	<210> 10 <211> 256 <212> DNA <213> Homo sapiens		
15	<400> 10	ctcgagggga ctttcccgga gactttccgg ggactttccg ggactttcca tctgccatct	60
		caattagtca gcaaccatag tcccggccct aactccgccc atcccggccc taactccgcc	120
		cagttccgcc cattctccgc cccatggctg actaattttt tttatttatg cagaggccga	180
		ggccgcctcg gcctctgagc tattccagaa gtagttagga ggcttttttg gaggcctagg	240
		cttttgcaaa aagctt	256
20	<210> 11 <211> 558 <212> DNA <213> Homo sapiens		
25	<220> <221> SITE <222> (546) <223> n equals a,t,g, or c		
30	<400> 11	gaattcggga cgagctgggc tgcagttggc gattccgcgc ggtgaaagca gccagtgcc	60
		agggctcttt cctgagtgca cctgggcctg ccgcccggcg atgccatggg gtcgtgcgct	120
		gcttttctac ttgccgcgct ctcaactgctc ggtgtactgg gagggtagcc tgggaggcgt	180
		gcctttatct ttcgaaccg ccgctcactg agacagtggc tagaagtgtc tcttggaact	240
		gtgagttagc cttaacctgt tatgccccca gagccctcag tggagcgccc gtactttgcc	300
		ggcatgacgt ttgatttccc ggtgataatc cgacgagttt gacagattga ggtagtgagc	360
		aaagtgtgcc gtcagttggt ggccacttga cttcgtgcgg accctggcct tgctcttgga	420
		agagatagtg ttcttagggc tggtttctact gtctcttaag actgaarggt ggarctggga	480
		tatagatgtg ttgtttcttt tcaaatacaa cctgcttarg tcgtcactcg aagggggggc	540
		cggtanccaa ttcgccct	558
45	<210> 12 <211> 715 <212> DNA <213> Homo sapiens		
50	<400> 12	cggatttcga gtgcttttct ccttacctcc accctcccc atgttttaat gcagccctcc	60
		aaaaatatct actgagtgtg gactctagac cagggcctgt gctaggatac aaagatgaat	120
		gaggcaccac ccttatcttc gagtagtata tgttttattt tattttattt ttttccctg	180
		ctgcctccct tgagttagtac atgttttagt aaggggaaca gacactaaag agtcttggtg	240
		atgatgagca aagtactgca tgagtaagta tctggggggc aagtgtcccc actaggactc	300
		ctgtcagatc tggaaaaggc ctgaggaatc tgatacatga cttaatgcag cgtatacttg	360
		cagcctggaa aactaagtaa tgacaaaata gacattcttg tcagtgtgag ccattctctg	420
		agtcctmaggg gagtacataa ttcaaacagc aattgggtcat tttggagttt gcactcttag	480
		cagtatacag tggagtgaat tttaagaatc aatttaattt cttttcagtt tttatgtaca	540
		taaaacctgc ttactacaag agaccagttt tattattttg tgttggttaa cattcataag	600
60		tatatttcat cataataagg ctccgtgaaa ttagtcatat tatcatttgc caataaagac	660
		atatatctga aaataaatgt tcctgaacct gaaaaaaaaa aaaaaaaaaa ctcca	715

	<400>	13					
10	gaattcggca	cgagccaaaa	caaaagaaac	ctttgggaggc	atgtgtcaga	acagagaaag	60
	tgtcctgggt	ttgcttatag	aatcaaatat	gttctcattc	tacctactgt	tttcattcta	120
	catagtgttt	tccttcttta	tagttttacg	tcctcttcct	aggaatgagt	ctattaagaa	180
	aatagggtgt	atcttttagc	tttggcattt	gacttttcagg	ataatagagc	tatctgctac	240
	tgacagaaaa	gctttgacaa	gtgttttaata	ctctgggatt	accttcattc	tacttttgca	300
15	atcattatgt	gaaccttagtc	ttccggtccac	atctayaggc	tagtawgtaa	accggttgac	360
	taaatccaaa	ctttaggcta	gggaaaaaagg	gtatactttc	tgggtttcgg	ttgtagatta	420
	tgtttagatc	taaycaaaac	aggacagtgg	tccaaacaga	aaattgctat	tttctgtatc	480
	ttgtaaatct	aggatttgag	tttttaagat	gaatttatgg	ttccctttct	gatatcattt	540
	ctcatctgca	gctcctaatt	cctggtacct	tgggtatgga	gtgaggagag	acaatggaca	600
20	gttttatata	agaaatggaa	gtaatgatac	tatctttcct	ggaatatattg	caggccccag	660
	aggagatgat	gagcaaggac	tgtttgacctg	tattacacac	aacagggttg	tagttactat	720
	cccagcaagg	aaagggtgta	tccttcttct	ttcatgcaca	ttatctatga	tgacctaaac	780
	gtttgattat	agtgagtggga	ctaaccacaa	caataaaaaa	aaaaaaaaaa	aactcgaa	838

```
25  <210> 14
    <211> 513
    <212> DNA
    <213> Homo sapiens
```

	<400>	14		
30	ctgcaggaaat tcggcacgag ggaacaactc catgttttgg taaggcccta gagaacatat			60
	atccagtgcc ttctcttttt gcctttgat tcatcatttt ggcaatttac tggaagatga			120
	cggttctggc caaaaggctg gtnttgTTTT tgggtcacat ttcttgctt ctctgcgtta			180
	gaatcttgga ttagatgatg gacatggtga agatctcagc aaacctattc actagaagat			240
35	catgtggatt ggaatcatac aatggggaac aaatggaaaa gagtactttt gaaatagtgc			300
	tggagaccac tgtgaccaca gaatgtcaag acacgtgctg ccattactgt tactatttgg			360
	aaaatacatt cttgtaaATG caaccttagg ggggtttgagg gggAAGTCTg ttgggAAAtg			420
	aATTGCaAg aaaataTTAc accTGAAAA aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa			480
	aaaaaaaaaa aaaaaaaaaa aaaaaaaACT CGA			513

```

45      <210> 15
        <211> 712
        <212> DNA
        <213> Homo sapiens

```

```

    <220>
    <221> SITE
    <222> (565)
50  <223> n equals a,t,g, or c

```

	<400> 15	
	gaattcggca cgagctggac aggaccggag aggacccgc gtaaccgcgg aacagacact	60
55	cccgccagcg gccgccgccc cggcactgct acgggacgag ccggagcgct tggccatggc	120
	ggcccgatcc gactggcgcg tgctgctgct gctgccagtc ctgctcctgc cggtgcagag	180
	ycgctcagag cccgagacca ccgcgcccac ccctacccca atcccgggtg gcaactcgtc	240
	aktgagcagg cccctgccca gcctcgagct ccacgcctgc ggcccatacc ccaaaccagg	300
	cctgctcctc ctgctggccc cgctggccct gtggcccatt ctccctgtagg gacgcccagc	360
60	cagccacctc taagtgcgcc ctgggactgg cctgcccatt tgagcaacag agacgcttga	420
	cagccgcccg cctccattcc ttgactccac ccagaaatcg gtccagaaaa ctgaattccca	480

	ccagcactgg	tttggagcaa	cgggacaccg	aggtttcacc	tccagggrtt	ccatggaaga	540
	gcctcaatgg	agatgccaca	tcctnactga	gttaaagatg	ggctgaggaa	cttgggtacc	600
	cacaagtytg	ccttgggrat	caaaagaaaa	tatttacctt	tagtttggtt	cattaaatgc	660
5	atgaagtcaa	aatatgaaaa	aaaaaaaaaa	aaaaaaaaaa	aaaaaaactc	ga	712
	<210> 16						
	<211> 652						
	<212> DNA						
10	<213> Homo sapiens						
	<400> 16						
	gaattcggca	cgagcaacag	tggggcactc	tgctcccagg	cagggtccac	tgggctgagc	60
	cgcacagcct	ggcttttggc	ttccctgact	gcaccaccca	catcasctgc	ctctagccct	120
15	taamatacaa	aacttccccc	agtcactggc	cgccaggctg	agttggggga	tgtgttacat	180
	ccctgggtcc	actggggggc	agtgttgccc	atggtgtttg	tgtgtgctct	gccgagaggc	240
	gttggagtgg	ctgtgtgggg	cggtgagcgc	cggcccagcc	tgatggaacc	cactgtacca	300
	ggcccaggcc	tcagcctctg	agaaggactt	ccctgtgtca	ctcactcata	catgtcctca	360
	ggacgtgaag	acattttcagc	agaccaaagt	ttcccttcgaa	tttccttcga	atcgtccaga	420
20	tacttggaga	catctcctcc	tcacctgtgg	gggtgtgggg	cagtccctagg	cgtgggggca	480
	gatgggtgga	cagctgtctg	tgccctgctg	ggggtgggca	gcccttgagg	cacacagtgg	540
	tgaagacatt	cctgaatatg	tctcaggctg	tagaaatcct	attttgtgga	aagatttttag	600
	agaatcatca	aaataaactt	ttaccaaata	aaaaaaaaaa	aaaaaaactc	ga	652
25	<210> 17						
	<211> 742						
	<212> DNA						
	<213> Homo sapiens						
30	<400> 17						
	ggtcgaccca	cgcgtctgat	atgatctcct	tatccttctc	cctttgattg	atctttttct	60
	ttgagctgat	ttgagctttc	ttctttttct	tgtagtgtgg	ggaatcagct	cagttacatt	120
	ttttactaag	ttaccacat	tctgacactc	cttgacagtk	ttaagatctt	cttctaacac	180
35	acttgaatag	aatggatact	ggaatctatt	ttgacagctg	ttgaaaatct	attctgttgt	240
	tacaggaggt	taaggaggtt	atttgaata	ctgggattat	ttaatgaacc	ttttgaaaag	300
	gtgtgcagac	tgttcaggca	aatagtatct	tttagaatta	aatgattttg	gttttcacag	360
	ttaaattatc	aaatgtaatg	cttttaagaa	ttatacacct	agtaatatct	ttcattaatt	420
	tctccaccag	tgtagtaata	gtacattaca	atgtttctca	ttaccgggtg	cttctaaaat	480
40	gcagggttag	agtcytaaag	tacagctagt	ctatkgccag	ctgtcccata	gataaccttc	540
	tcytaaag	tgaccttkgr	gcaatttycat	aaagaataaa	tatttctagt	tttttgttgc	600
	tgaactgcta	aaagatggtt	ctatacatgt	aacagggtgg	tttagttggg	ttgctttcac	660
	tgaaatttga	ttcaaataaa	gcattgcatt	attttacctt	tggaattata	aaaaaaaaaa	720
45	aaaaaaaaaa	aaaagggcgg	cc				742
	<210> 18						
	<211> 1219						
	<212> DNA						
50	<213> Homo sapiens						
	<400> 18						
	aacgcactca	atatttcagaa	gtttgaattc	taccactctc	aaacacagtt	caaaagatag	60
	ctgtttgaga	atgcttctta	actaatacta	gtacaatatc	ttcaataatg	tatgtacctt	120
55	atagaaaatc	ttgaacagta	caagattttc	ataattaaag	catgcaaaac	tgcttgggct	180
	ctttgattcc	aggtgtcctc	ttctcccttc	tgcttttgcc	atctatgttc	aatataattc	240
	taaccacgtc	taagtatgga	gaaaattcct	accctgcctg	cttttatagc	tcataaaatt	300
	tccttgatc	agctatcact	tttctggtag	gtgtagtctg	atttctgtct	gtcatgcctt	360
	tgccacaatc	ctttctttga	agagtaggta	aaagatctat	taaagtgtta	atcacattgc	420
60	tctaatatat	aaagcctcca	gtggtttccc	atatcactct	gtaaaatgcc	ccttgccagc	480

	ctctcccatc aacctcgctt tttctgttct tgtatatgca catctcttcc tgagccctta	540
	ttgccatcct catgtgggga tgtttctgtc tcagagatag tctttattca ggtcccactc	600
	tgacagctctc tccagagggg ctgctttcac cacccttct aagtaagcct ctctaaacac	660
	ctctatcata ttctatccct tagccagcac taattttttc ataatgctta ccactaactg	720
5	aaatttactt tatcatttaa tctcttccct attagaatgt aagctcgtaa gggaggggca	780
	gctctgtagt ttattcatta ttgtatgtcc ctcacctaatt cctatgagtg tctggcccat	840
	attagggtat gtaataaata ttacttgagg aatgaatgaa tttaacatac taccaattct	900
	ctgagtgaact ctttttaaaag ccttcacatc cattcacact ttcttgtctt tcatatgggc	960
	atgtccaatc acccttccat gaatatctgt acctgttaca aagagaggac taggttcctg	1020
10	gagttcatag atgtaaaca catcctaggg ktagcaaaact ggtgggccct gagccaaatc	1080
	ctggcctgca catgtatttt gtttgakttg tacaatgttt gttataaatg aactggctga	1140
	taatatTTTT taattggaaa tgtttacatt aaaaacctar acttctagct gctcttaaaa	1200
	aataaaaaata cggctgggc	1219
15	<210> 19	
	<211> 874	
	<212> DNA	
	<213> Homo sapiens	
20	<220>	
	<221> SITE	
	<222> (461)	
	<223> n equals a,t,g, or c	
25	<400> 19	
	ggtcgaccca cgcgtccgag caattgaatc atctgcccac ggataagctg ctgggtgagag	60
	cagagttggg atttgaagtc gagtttagacc ccagtgtatc cagtcttgac gattaaattc	120
	ttccagcttt cattttttcac tgagataatg gtagtgatag tactgacctc taatgtgtgc	180
30	atttgtgggt atgtgggtcca ttcagcttta atccccagaa gacaaggctt attccttttc	240
	ttatttttgg tcatgtttta tttttccatt gcttttaaca ggattaccaa aggcacactc	300
	agtagtcagt aaacacattt ctaggaaagg tgttgtgtca tcatgccaca tattcatact	360
	ttcctgggtt ggaaaataga tcatcagtaa aaacatacag gaaaaatgaa tcttgccaat	420
	gcaattgtta acctacaacc ataataatacc ttaagtatat ntttgcacat aagtataaca	480
35	tgcgatttaa aacaataaac cagattgaga tctaaggagc attttgtaag taattactaa	540
	tgtttatttt agagagatca cacaacttca aataaaaact gacatagatt gaacaccttg	600
	agaataaact ttagtgccaa atggaaaata attttttaca agtaaatgtg aagaacaatg	660
	tgaactttct ataattatat acagraaata tactgatttg ccaaaatgag taattttgat	720
	atattaatat ttcacttata agaatgcata ccacctgatc caggatggga tccaggaaca	780
40	gaaaaagaac attagktaaa aatgacagaa atctggaatat agtatagagt agctaaaaac	840
	aaaccaaaaa aaaaaaaaaa aaaaaagggc ggcc	874
45	<210> 20	
	<211> 464	
	<212> DNA	
	<213> Homo sapiens	
	<220>	
50	<221> SITE	
	<222> (21)	
	<223> n equals a,t,g, or c	
	<400> 20	
55	caaacccttc agtggatgag nccaagtcgc agaaagcatt ctgttgacag atgaacagcc	60
	gaaagctggc cagaccctcc tgkatgcact cccwgcceck tktatcagaa acacaggcaa	120
	ggaaattgga actgccaccc agcccagcat ggtggctcaa ttggttggtt gcgttgtag	180
	ttgtctcttc gttttgttaa ggtttttaat aagtacgttt ggcataatgt cttttaatgg	240
	gtttgttaata tttgtaacgg ttttagcagc ctataacttt tcagctgggt cttttactta	300
60	gggaaaaaaa caatttgtaa atacagaaca ttgttttaaa gacataacca tagaacatag	360

cttcctgttt gtggattttg tttcctatat attcaaagta aaatgactta caggaaaaaa 420  
ataaaaaaaaa aaaaaaaaaa aaaaaaatcg gggggggggc ccgg 464

5 <210> 21  
<211> 637  
<212> DNA  
<213> Homo sapiens

10 <400> 21  
gattttcctg cttgcatcat ttctagcaca gagctggagg aaatggcgag gtgcagggtg 60  
ccgctggccm tgctgttcta catgggagca agacagctgc taggtgaagg ggaatgacca 120  
ggcagccaca gggaggacat gtggcctcag gaagcctggg tgtgtatcct gggtctgcta 180  
ggaacacgtg tggggccttg tgtgggtgac tctctggctc cccaagcctc cctttcctac 240  
15 tgttatatcc ttaaagtgcc tctgaggcca aagcctttgt ggcaattgtc aaatgagtcc 300  
atatgcagtg agtaccgtgt tgaggaggga caaggtcacc aagagctgag aatgtttctc 360  
cgactgatga gacctagata ttgggtacat ggaggtcccc ggtecccttg tgattcctgc 420  
agcctgttgc ttccttgccg ggaccccgcc tcagctcaga aagccaattc cctagattcc 480  
aaaggccttc ccagaccaat tagcatgtcc tgcagctgtc agctccctgt gcctagcctg 540  
20 gacctcagct catgtctagc acccagcttc ccaacccac acatattcac aaataaaaga 600  
aaataacaaa tgaaaaaaaa aaaaaaaaaa aaaaaat 637

<210> 22  
25 <211> 752  
<212> DNA  
<213> Homo sapiens

<400> 22  
30 gaattcggca cgaggggatt acaggcatga gccaccatgc ccggccatat aaagcattta 60  
ggatagttag ttgctatttt tattttattta ttattgttgt tgttattata ttactacttt 120  
atcccatttc acaaggatgg catgttgcca acattgtctt tctaaagaat atctctgac 180  
acatccttgt tctattaaaa accttttgaa agctccctct tacctttaga agaaattgga 240  
acttcatgat tctcatgggt ctggctccag cactgagtct ggaatgctag tgtgagatga 300  
35 ggccttagaa gtcattccagc tgaactcctg gaatttttat agatgaataa atgtagcatc 360  
cagacatttt tcytgttgca cccctgtamg ccatgtcctc tccagactc ctggataaga 420  
ctgrcagaca tcaccattct cttaaaccag aactacactt gccttcattc atttgatcac 480  
ctggttccag gtaactcatg agctttgtag ctteccctct ctcagacctt ccaagggaaga 540  
caatggcata attttcccca tatgtctctaa ttagcaacct ttccctgccc ttctgtgggt 600  
40 gggcagggcc ggacacagtg ggtcacacct gcaacctgta atcccagcac tttgggaggc 660  
tgaggtgggc agattgcctg agctcaggag ttcaagacag tctgggtaac atggcaaat 720  
cctgtctcaa aaaaaaaaa aaaaaaactc ga 752

<210> 23  
45 <211> 492  
<212> DNA  
<213> Homo sapiens

50 <220>  
<221> SITE  
<222> (486)  
<223> n equals a,t,g, or c

55 <400> 23  
aagctggact cgcgcgcttg caggtcgaca ctagtggatc cmaaagaatt cggcacgagc 60  
aaggacccag aagtaggggt ttggcctagg taacggggca gagatgtggt tcgagattct 120  
ccccggactc tccgtcatgg gcgtgtgctt gttgattcca ggactggcta ctgcgtacat 180  
ccacaggttc actaacgggg gcaaggaaaa aagggttgct cattttgggt atcactggag 240  
60 tctgatggaa agagataggc gcatctctg agttgatcgt tactatgtgt caaagggttt 300

	ggagaacatt gattaaggaa gcatttttctt gattgatgaa aaaaataact cagttatggc	360
	catctacccc tgctagaagg ttacagtgtg ttatgtagca tgcaatgtgt tatgtagtgc	420
	ttataaaaaa taaaatgaaa aaaawrmaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa	480
	aaaaanaaaa aa	492
5	<210> 24	
	<211> 532	
	<212> DNA	
10	<213> Homo sapiens	
	<400> 24	
	actcatataa gaaagcagta cgcgcgagta cgggtccgaa ttccgggtcg acccagcgct	60
	ccgcccacgc gtccgcacct cccttggtcg tggggagggg cttccatgcc ctgtgtggct	120
15	ctcgggtggg ctgtcgcacc acactgctct tcctttctct tcacgaatca cgcaagcctc	180
	ctagtcagtt ctgatgagat aacctggata tcttggttgc cggatgaagga tttacatgct	240
	tattatgggt tttttgttgt tgttgttgtt tgggtttttt tttgatggga gcctcagatc	300
	gccgctgttg ctaatcatcc atcttggtccc tgccccaca tttctgcaaa tttaaatatg	360
	agatttgtcc ccttaggtgc acagtccaga ccccatccag tccagctcct tttaaagcca	420
20	catggaaagt cagctgagaa tggtttggga gccaggtgc gctgtcttcc gccctgccct	480
	ctccctgaaa taaagaacag cttgacagaa aaaaaaaaaa aaaagggcgg cc	532
	<210> 25	
25	<211> 920	
	<212> DNA	
	<213> Homo sapiens	
	<220>	
30	<221> SITE	
	<222> (907)	
	<223> n equals a,t,g, or c	
	<220>	
35	<221> SITE	
	<222> (914)	
	<223> n equals a,t,g, or c	
	<220>	
40	<221> SITE	
	<222> (920)	
	<223> n equals a,t,g, or c	
	<400> 25	
45	gtcggaaattc cgggttcgac ccacgacgtc cgcaaaatta acatcaaaaa ggtatatact	60
	ttttaaaaaa aatttacttt tattgatgtg tactcttctt attgatgagt taattccata	120
	aatctctact tagtttaact tattggatca aattatcttc agcatgtata tctggggaaa	180
	aaaggtccga attttcacat ttatatattaa acttcaattt tttatattta aacttcaatt	240
	tttttagcaac agctgaatag ctttgcggag gagtttaata gttacacatt catgctaata	300
50	tacatttctt ttaaacatcc acaaattctt aaaaagrttg aatcagtaaa tttcatttca	360
	gctaaaaatg gagtctaata tattgtttca aaagatacat ttttaccac cataaatgtt	420
	acaatatctg aatatgcttt gtcaaaactat ccctttatgc aatcgtcttc atattgtttt	480
	tatgattcta atcaagctgt atgtagagac tgaatgtgaa gtcaagctcg agcacaataa	540
	gataatgcac gatgagattg cctaccattt tataggatat ttactatgta tttatacgtt	600
55	aagacctcta tgaatgaatg tatcagagaa tgtctttgta actaactgtt taattcaatc	660
	tgtataaaaa atctaactaa ctaactcatt tatttctatt aaaaaggtat tgtcctttag	720
	gcgggggaatt ggaatccttg ctgcactgtt gcagtcattc tgaaaggacc tttccctgta	780
	cttacccttc aacatgcttc aatcttatca acgctacatt ttgtattttt caaacaagta	840
	taaattctgc aataaagaga tgtagttttt ttttaaacaa aaaaaaaaaa aaaaaaaaaa	900
60	aaaaaanggg ggnccccc	920

<210> 26  
 <211> 917  
 5 <212> DNA  
 <213> Homo sapiens  
  
 <220>  
 <221> SITE  
 10 <222> (434)  
 <223> n equals a,t,g, or c  
  
 <400> 26  
 15 gaattcggca cgagggtttca ttgccctcaa cattctctgt tcttcaccga atcatgtctg 60  
 tttcctccaa cctctggcaa acactgatct tgttactgtc tttgtggttt tgcctttttc 120  
 cagaatgtca tatagttgga atcatacaat tgtgcagact ttttagattg ccttctttca 180  
 cttagtaaca tttaagtttc ctccaccctt tttcatggct tgatagttca tttcttttaa 240  
 ttgctcaata ataaatattc cattatctag atagaacggt ttatctacct agtgaaggac 300  
 20 atctcaattg cctccaagtt taggcaaata taaacaaagc tgctatcagg atttttcaca 360  
 gaggaagaaga cagtgggatc caaaactgaa tggctctatca ataaatgacg catggtacat 420  
 ctacacccat granccattg tgcatccatg agaaaaatcc agatgtagga aggtatgtat 480  
 aattttgcag aaaagagtat gtaactggaa acaccaarga aaaaaggaaa tggatctata 540  
 tatttaggtg gagatattta tgtggtcgca gaagaaatat attattattc atactagata 600  
 25 gttaaatgtt gccttttggtg ggcaagaaag gtaaaaaggg agaagggagc ccaacaaaaa 660  
 gaggaagagg aagaaaaaaa aactgcacta agaaaaatct tttaaaagta tgtgatcaca 720  
 gccaggtgca gtggctgaca aatgtaatcc cagctacttg ggaggctgag gcaggagaat 780  
 cgcttgaacc caggaggctg aagttgcagt gagctgagat catgccattg cactccagcc 840  
 tgggtacaga gactctgttt caaaaaaaaa aaaaaagtat atgatcacat ctgtgttaac 900  
 30 ttacagacta gtctcga 917  
  
 <210> 27  
 <211> 662  
 <212> DNA  
 35 <213> Homo sapiens  
  
 <400> 27  
 40 gaattcggca cgagggttccc atggcacttt atatgtgtgc atagagagcc agggagcagt 60  
 ggggttcagg gtgggcccct gctatgtgct gcagagctgg tgggtcacag tctccccagg 120  
 tgatggtggt gttaataatc atctaggcc cgtgggtggt ggtgaggatt gatgcatgag 180  
 aaagttgagg cggggggcct ggcatggagc agggctcagg ccgcttgta cccaggctca 240  
 tgtcagccct ccggagcctg tgggtgtata ggggaagcgc aggggttctt cagccagagg 300  
 gacaggttca rggcctgctg atgcccttct ctggttttgg gaccttgagc aagtccccct 360  
 gccttttggg gctgtgcttc ggtttcttct tctataagaa ggaggtgatg atgtaaccca 420  
 45 cccaccagc ccctctacct cgcgcatcag ggtagcaggc gagctagcac tgtggcacca 480  
 ggagtggagc tggcccctgg cgggcccacg ctggagaggc atcgccatct ctgctgcccc 540  
 cctgtggcgt catcatatca acctgccagt cccctcacc tgggtgttaat ctcccagagg 600  
 atggggactg rttctgcata ttctttgcta aacaaagacg ctagtgtggc tgtggctctc 660  
 50 ga 662  
  
 <210> 28  
 <211> 699  
 <212> DNA  
 55 <213> Homo sapiens  
  
 <400> 28  
 60 gattcggcac gagaaacttt taaatcttta gttatttctt aatacttaga acacttaaac 60  
 aaaactttac aaaacaaaag agcagaataa ttagatcctt tcaggagaat atgacttttt 120  
 tttcctaagc acactggacc atagaggaag accaaaggaa tgtacagttg cctgctcctt 180



	cctgacttgc	tgtatttgac	tctgtcccca	ctgggtgggg	caatgctatt	aacccccacac	240
	tttaacgtgg	caaatacccca	gaatctgttg	gctgggtctct	ggctagagaa	tgagcacagt	300
	ttcacccctta	tggtccaga	aagagcaaga	acacaccact	gccagccaga	agagagaaaa	360
	gtcttgttct	gtctctttcc	cattgtccca	aatagccaag	cacaggttca	accaccccaa	420
5	atgccaccct	tctgctgtgc	agcagccaag	gaaaagaccc	aggaggagca	gctccaagaa	480
	cctctgggca	gtcagtgccc	agatacttgc	cccaattctt	tgtgtccaag	ccacactcag	540
	ctgacaaaag	ccaacacttt	gtctctcttt	tttttttttt	cttttttttt	gagcagagtt	600
	tcactcttgt	cacccaggct	ggagtgcaat	ggcaggatct	tggtcattg	caacctccac	660
	ctcccgggtt	caagcaattc	tcctgtctca	gcctctcga			699
10							
	<210> 29						
	<211> 1637						
	<212> DNA						
15	<213> Homo sapiens						
	<220>						
	<221> SITE						
	<222> (726)						
20	<223> n equals a,t,g, or c						
	<220>						
	<221> SITE						
	<222> (727)						
25	<223> n equals a,t,g, or c						
	<220>						
	<221> SITE						
	<222> (728)						
30	<223> n equals a,t,g, or c						
	<220>						
	<221> SITE						
	<222> (899)						
35	<223> n equals a,t,g, or c						
	<220>						
	<221> SITE						
	<222> (901)						
40	<223> n equals a,t,g, or c						
	<400> 29						
	aaatgtgcca	cgtcttctaa	gaagggggag	tcctgaactt	gtctgaagcc	cttgtccgta	60
	agccttgaac	tacgttctta	aatctatgaa	gtcgagggac	ctttcgctgc	ttttgtaggg	120
45	acttcttttc	ttgcttcagc	aacatgaggc	ttttcttgtg	gaacgcggtc	ttgactctgt	180
	tcgtcacttc	tttgattggg	gctttgatcc	ctgaaccaga	agtgaaaatt	gaagtctctc	240
	agaagccatt	catctgccat	cgcaagacca	aaggarggga	tttgatgttg	gtccactatg	300
	aaggctactt	agaaaaggac	ggctccttat	ttcactccac	tcacaaacat	aacaatggtc	360
	agcccatttg	gtttaccctg	ggcatcctgg	aggctctcaa	aggttgggac	cagggcttga	420
50	aaggaatgtg	tgtaggagag	aagagaaaagc	tcatacttcc	tcctgctctg	ggctatggaa	480
	aagaaggaaa	aggtaaaatt	ccccagaaa	gtacactgat	atttaatat	gatctcctgg	540
	agattcgaaa	tggaccaaga	tcccatgaat	cattccaaga	aatggatctt	aatgatgact	600
	ggaaactctc	taaagatgag	gttaaagcat	atttaaagaa	ggagtttgaa	aaacatgggtg	660
	cgggtgtgaa	tgaagatcat	catgatgctt	tggtggagga	tatttttgat	aaagaagatg	720
55	aagacnnta	tgggtttata	tctgccagag	aattttacata	taaacacgat	gagttataga	780
	gatacatcta	cccttttaat	atagcactca	tctttcaaga	gagggcagtc	atctttaaag	840
	aacattttat	ttttatacaa	tgtcttttct	tgttttgttt	aattattttt	atatatttnt	900
	nctgactcct	atttaaagaa	ccccttaggt	ttctaagtac	ccatttcttt	ctgataagtt	960
	attgggaaga	aaaagcta	tgggtcttga	atagaagact	tctggacaat	ttttcacttt	1020
60	cacagatatg	aagcttttgt	ttactttctc	acttataaat	ttaaaatgtt	gcaactggga	1080

atataccacg acatgagacc aggttatagc acaaattagc accctatatt tctgcttccc 1140  
 tctattttct ccaagttaga ggtcaacatt tgaaaagcct tttgcaatag cccaaggctt 1200  
 gctattttca tgttataatg aaatagttta tgtgtaactg gctctgagtc tctgcttgag 1260  
 gaccagagga aaatggttgt tggacctgac ttgttaatgg ctactgcttt actaaggaga 1320  
 5 tgtgcaatgc tgaagttaga aacaaggtta atagccaggc atggtggctc atgcctgtaa 1380  
 tcccagcact ttgggaggct gagggggcg gatcacctga ggttgggagt tcgagaccag 1440  
 cctgaccaac acggagaaac cctatctcta ctaaaaatac aaaagtagcc gggcgtgggtg 1500  
 atgctgcct gtaatcccag ctacccagga aggctgaggc ggcagaatca cttgaacccg 1560  
 10 gagggggagg ttgcggttaag ccgagatcac ctccagcctg gacactctgt ctcgaaaaaa 1620  
 aaaaaaaaaa aactcga 1637

<210> 30

<211> 2142

15 <212> DNA

<213> Homo sapiens

<400> 30

aattcggcac agagacgcgg gtccccgggt ctgacaggag cagcctgtgg gcaccgcggc 60  
 20 ggtagttaga ggcgggagag ggtccgtagc cgcgcgccc tgccccgcca tgggcctcct 120  
 gtcggaccgc gttcgccggc gcgcgctcgc ccgcctagtg ctgcgcctca acgcgccgtt 180  
 gtgcgtgctg agctacgtgg cgggcatcgc ctggttcttg gcgctgggtt tcccgcgct 240  
 gaccagcgc acttacatgt cggagaacgc catgggctcc accatgggtg aggagcagtt 300  
 25 tgcggggcga gaccgtgccc gggttttgc cggggacttc gccgccacc gcaagaagtc 360  
 gggggctctg ccagtggcct ggcttgaacg gacgatgcgg tcagtagggc tggaggtcta 420  
 cacgcagagt ttctcccga aactgccctt ccagatgag acccacgagc gctatatggt 480  
 gtcgggcacc aactgttacg gcatcctgcg gggccgsgt gctgccagca ccgagtcgct 540  
 tgtgtcacc gtgccctgtg gctctgactc taccaacagc caggctgtgg ggctgctgct 600  
 ggcactggct gcccaacttc gggggcagat ttattgggcc aaagatatcg tcttcctggt 660  
 30 aacagaacat gacctctcgg gactgaggc ttggttgaa gcctaccacg atgtcaatgt 720  
 cactggcatg cagtcgtctc cctgcaggg ccgagctggg gccattcagg cagccgtggc 780  
 cctggagctg agcagtgatg tggtcaccag cctcgatgtg gccgtggagg ggcttaacgg 840  
 gcagctgccc aaccttgacc tgctcaatct ctccagacc ttctgccaga aagggggcct 900  
 gttgtgcacc cctcaggga agctgcagcc cgaggactgg acatcattgg atggaccgct 960  
 35 gcagggcctg cagacactgc tgcctatggt tctgcggcag gcctccggcc gccccacgg 1020  
 ctcccatggc ctcttctcgc gctaccgtgt ggaggcccta accctgcgtg gcatcaatag 1080  
 ctcccgccag tacaagtatg acctggtggc agtgggcaag gctttggagg gcatgttccg 1140  
 caagctcaac cacctcctgg agcgcctgca ccagtccttc ttctctact tgctccccgg 1200  
 cctctccgcg ttctgtctcca tcggcctcta catgcccgtg gtcggcttct tgctcctggt 1260  
 40 ccttggtctc aaggtcttgg aactgtggat gcagctgcat gaggctggaa tgggccttga 1320  
 ggagcccggg ggtgcccctg gcccagtggt accccttccc ccatcacagg gtgtggggct 1380  
 ggcctcgctc gtggcacctc tgcgtatctc acaggccatg ggactggccc tctatgtcct 1440  
 gccagtgtg ggccaacacg ttgccacca gcaacttcca gtggcagagg ctgaggctgt 1500  
 ggtgtgaca ctgctggcga tttatgcagc tggcctggcc ctgccccaca ataccaccg 1560  
 45 ggtggttaagc acacaggccc cagacagggg ctggtatggc ctgaagctgg tagccctgat 1620  
 ctacctagca ctgcagctgg gctgcacgc cctcaccaac ttctactggt gcttctgct 1680  
 ggccaccacc atggtgcccc ctgctgcgct tgccaagcct catgggcccc ggacctcta 1740  
 tgctgccctg ctggtgctga ccagcccggc agccacgctc cttggcagcc tgttctgtg 1800  
 gcgggagctg caggaggcgc cactgtcact gggcaggggc tggcagctct tcctggcagc 1860  
 50 gctagcccag ggtgtgctgg agcaccacac ctacggcgcc ctgctcttcc cactgctgtc 1920  
 cctgggcctc taccctctgt gggtgctttt ctggaatgtg ctcttctgga agtgagatct 1980  
 gcctgtccgg gctgggacag agactcccca aggaccccat tctgcctcct tctggggaaa 2040  
 taaatgagtg tctgtttcag carmaaaaaa aaaaaaaaaa aaaaaaaaaa aatgaccctc 2100  
 55 gagggggggc ccgggtaccc aattggccct atgaagaggc ga 2142

<210> 31

<211> 1564

<212> DNA

60 <213> Homo sapiens

<400> 31	
	ggcacgagcc ttaggggaac gtggctttcc ctgcagagcc ggtgtctccg cctgcgtccc 60
	tgctgcagca accggagctg gagtccgcatc ccgaacgcac cctcgccatg gactcggccc 120
5	tcagcgatcc gcataacggc agtgccgagg caggcggccc caccaacagc actacgcgcc 180
	cgccttccac gcccgaggcc atcgcgctgg cctacggcag cctcctgctc atggcgctgc 240
	tgcccatctt cttcggcgcc ctgcgctccg tacgctgcgc ccgcggaag aatgcttcag 300
	acatgcctga aacaatcacc agccgggatg ccgcccgtt ccccatcatc gccagctgca 360
	cactcttggg gctctacctc tttttcaaaa tattctccca ggagtacatc aacctcctgc 420
10	tgtccatgta tttcttcgtg ctgggaatcc tggccctgtc ccacaccatc agccccctca 480
	tgaataagtt ttttcagcc agctttccaa atcgacagta ccagctgctc ttcacacagg 540
	gttctgggga aaacaaggaa gagatcatca attatgaatt tgacaccaag gacctggtgt 600
	gcctgggect gagcagcatc gttggcgctc ggtacctgct gaggaagcac tggattgcca 660
	acaacctttt tggcctggcc ttctccctta atggagtaga gctcctgcac ctcaacaatg 720
15	tcagctaggc ctgcctcctg ctgggcgggac tcttcattcta cgatgtcttc tgggtatttg 780
	gcaccaatgt gatggtgaca gtggccaagt ccttcgaggc accaataaaa ttggtgtttc 840
	cccaggatct gctggagaaa ggcctcgaag caaacaactt tgccatgctg ggacttgagg 900
	atgtcgtcat tccagggatc ttcattgcct tgctgctgcg ctttgacatc agcttgaaga 960
	agaataccca cactacttcc tacaccagct ttgcagccta catyttcggc ctggggcytt 1020
20	accatcttca tcatgcacat cttcaagcat gctcagttat gaggagtcaa atcctaagga 1080
	tccagcgcca gtgacagaat ccaaagaggg aacagaggca tcagcatcga aggggctgga 1140
	gaagaagagc aaatgatgca gctggtgccc gagcctctca gggccagacc agacagatgg 1200
	gggctggccc cacacaggcg tgcaccggta gagggcacag gagggcaagg gcagctccag 1260
	gacagggcag ggggcagcag gatacctcca gccaggcctc tgtggcctct gtttcttct 1320
25	ccctttcttg gccctcctct gctcctcccc acaccctgca ggcaaaagaa acccccagct 1380
	tccccctcc ccgggagcca ggtgggaaaa gtgggtgtga tttttagatt ttgtattgtg 1440
	gactgatttt gcctcacatt aaaaactcat cccatggcma aaaaaaaaaa aaaaaaaaaa 1500
	aaaaaaaaaa aaaaaaaaaa aaaaacaaaa aaaaaaaaaa aaaaaaaaaa aaaaaggggg 1560
30	gggg
<210> 32	
<211> 1631	
<212> DNA	
35	<213> Homo sapiens
<400> 32	
	cttaggggga gccctgggtgc tacttgcttg aagttttcag tgtaagtacc ctgatgcctt 60
	ttggaccttg ggatcagatc aagagttttg gagatcaggt accaaggaaa taaggacagt 120
40	ctagctgcct caagtggagg gccctttgca tagctctcct tccccctcac tgaagctggg 180
	tagcctattg gggttgagag ggaaaatgtg aaatctcaga atttatctcc cttagaagag 240
	agccagtaac ttatgtacaa ggatgaaaaga aaggtcgcag cagtagcttt ggggaaaggg 300
	aggaagatata ggcacttctc caaccccgga aaacattgct tttgaaaact gctgataaaa 360
	tatgagccgg ttattacttc tgtttgggag actgtgctct ctgtggtgcc tctctggct 420
45	ctactccaca gataccagac ctcttctaag aggatgagca gaccagcttt gaggttgacc 480
	tgtttctctt tgtctgcctt cccaaaacac cagccccag gaagacatta agcagcctta 540
	agcttaaat cctactccct cttccaaatt tggctcactt gccttagatc caaggcaggg 600
	aaaggaaaag aaggggggtc tctggcttta ttactccctt aagtctttac tctgacttcc 660
	ccaaacccag aaagattttc tccacagtgt tcatttgaaa gaggagtatt ttgtccatt 720
50	ttccccttcc tcattatcaa acagcccag tcttcctgt ctctgctaag aaagtagagg 780
	catgatgac tgcctctcaa ctgccctaag tcctagctaa gtatcagggg aaaaaaaaaa 840
	aaaaaaaaagcc taacaaatgg gattagacta gggctgcaag tagtgaggat tttgttgata 900
	cctctgctgg gatgtgtgct tccccatc ttgccttcag gaattacact gtgccttttc 960
	cccagggata tgggctctgt ctaccagtg ctccagtttc ccggtaactg ctcttgaaca 1020
55	ttgtggacaa gggcaggctc tcatattttt gatcatccct ttctcccag gaaatcccat 1080
	agcccttacc tagagtctag ggcacaaaaga cttcggggaa gataactga gattgacctg 1140
	aggagacatc tacacacacc agtggcagct cccccaggc ctgcttcccc ttcctaagtc 1200
	tgtcatcttc tggaagggat ggggtgtgct ccaatctctg gtgcctaaaa acccaagttt 1260
	atttctctct taacactggc aataaccagt ccacaccact gttgcctttt aaaacctctt 1320
60	aataatctca tgctgtgttt gttttgattc caatccaatt atcaccaggg ctgtgtgggt 1380

	aaatgctttt aaatgctctc tcatcttggt cttccccctc accccccact cttaggtagt	1440
	tatgatgcta atcttgtccc taagtaagtt tcttcctgct ccttttgtat cttcctttct	1500
	tgtctttcct cctacctttt gtctcttggt gttttgggac tttttttttt ttttttgcc	1560
	ttttgtacaa agattagttt caatgtagtc tgtagcctcc tttgtaaaacc aattaaaaag	1620
5	ttttttaata a	1631
	<210> 33	
	<211> 978	
10	<212> DNA	
	<213> Homo sapiens	
	<220>	
	<221> SITE	
15	<222> (2)	
	<223> n equals a,t,g, or c	
	<220>	
	<221> SITE	
20	<222> (27)	
	<223> n equals a,t,g, or c	
	<400> 33	
	angagttgca tgcaagsgta agttggnccc ytsgrggatc tttagagcgg ccgcccctttt	60
25	tttttttttt tgcattgtctg agtttgtgga ataagattca tatttactac aagtaatgga	120
	attggagatt cagaggggag aaagtcactt atcacattag tgtaattttc tgatggtagg	180
	attatggaga gtttttaggtt ttcccttttt ttccccaact tctctccctt cagtatttta	240
	aaaataacat tgtgtgggtt gttttttttt gtttttgatt gttttttgtt tttcaaacag	300
	gtctcactcc tatccatgta ggctagagtg cagtagtgca atcttggtc actgcagcct	360
30	cgacttcctg agctcaggtg atcttcccac ctcagtctcc tgagtagctg ggactccagg	420
	tgtgtgccac catgcctggc taaattttttg tatttttatt agatacaggg tctcaccatg	480
	ttgccagac tggtcttgaa ctctggggcc tgcccacctc agcctcccaa agtgctagaa	540
	ttacaggcat gtgccaccat atccagccta ataacattgt ttttaattgt cattaagtca	600
	tcccaccctc tcagtcttg agaaagcctc caagagggac agaatacagtt gcaaagtacc	660
35	atctctgacc ctgagacatg gatattattt gttcatttaa atgtcacctg aaaaaccac	720
	tcaactcaaat ggtctgtgaa gcttgcaaaa acaggaatgc ttaccctcct gggtcctgaa	780
	tttttggttc tcttggaact tttgaaattc ttcttttcca gaaaggagcc ctctttctat	840
	ttcccctcaa agttgtgact tgaccctcac atccctttct tctccagggc cccttgataa	900
40	gattctttta aaatttcttt ggagggcatc ccttttagga agacggacgc gtgggtcgac	960
	cgggaattcc ggacggta	978
	<210> 34	
	<211> 898	
45	<212> DNA	
	<213> Homo sapiens	
	<220>	
	<221> SITE	
50	<222> (402)	
	<223> n equals a,t,g, or c	
	<220>	
	<221> SITE	
55	<222> (452)	
	<223> n equals a,t,g, or c	
	<400> 34	
	gaattcggca cgagattatg tagtagatgt cactagaatt cttgaaattt gtcttcaagt	60
60	catggcagta tttcagtatc gtccttttgg gattgcctga gtgatactca agagtttagac	120

	tagttttatc tgggtttctt gaagaaccgg ggacacctca ctggcttatg ttgaatttct	180
	gcactgcagg gaccaactat aaatgggtgt tttgggtttt tacgtgttaa gagctttaaa	240
	atgtaattct tcctatcatt catgcacaaa tgttctcaca caaattgctt cacagattga	300
	taaaactttg aataattttt ccctgaagaa atgttgaact tttctgcaag ctgttggaat	360
5	kggagcgcgt gttgaaaggc ytgaakggga ccgtactgta cngcctawtt cttttaaaaa	420
	aaattawgat ttcyattttt watycattta cngatgactg aatakgyca ggccagaaaa	480
	tatcccccta tttcaaaatg cagcaatcta taaacaaaat acttgccatt tttctaaatg	540
	acaccttttt ctataatttg tatagaaaat taagtgaag ggccaggcac cgtgtaacgc	600
	ctgtaatccc agcactttgg gaggccaagg cgggtggatc gcctgaggtc agtagttcaa	660
10	gaccaccctg gccaacatgg cgaaactcca tctctactaa aaatacaaaa caattagcca	720
	gggtgtgtgg cagacgcctg taatcccagc tacttgggag gctgaggcat gagaatcact	780
	tgaacccagg aggcagaggt ggcagtgagc tcagatggcg ccattgcact ccagcctggg	840
	taacaagagt gaaaactgaa gctgtctcaa aaaaaaaaaa aaaaaaaaaa aactcgga	898
15	<210> 35	
	<211> 754	
	<212> DNA	
	<213> Homo sapiens	
20	<220>	
	<221> SITE	
	<222> (311)	
	<223> n equals a,t,g, or c	
25	<400> 35	
	cagcctcatc tcctgttggc cccttgtatg taccctgtgt ttgagttgta atgaacccct	60
	gcttgtccat aatctttctt ttaactcctg tgcttctctc tcaccccttg cagagccttc	120
	actttctgct taaagtggac cttgacttct ctttatcttg ctccatttgc acctgaaact	180
30	tgtcctcaac tgcagtgcta attccttggg aatgttttat aactttgtca ggcagctaga	240
	cactgtaagt atagaacatg ctgggaaatc caaattaaaa atgacagttg gcacaaagct	300
	gacttctggg nagggaccaa ggaaaagtag ccagagtggc aggatagctg cttccatcac	360
	ggattgccag caatgtaaag cgtagactcc agaggaaacag tgctaactta aattaactat	420
	gcaggcatca gtacttctgg ttctgatggc ccggggattt ctaagtagta gtgagtctca	480
35	gcattatttg ttatacagtc tactgctaga tgaacaaggc taagtctaca gagaaggtaa	540
	atttagaaa ttaggccccg tctctgctaa gaatacaaaa aattagccgg gcgcggtggg	600
	gggtgtcctgt cgtccagct actcgggagg tgacgcagga gaatggcgtg aaccggggag	660
	gcggagcttg cgggtgggccc agatagcgcc actgcagtct ggccctgggcg aaagagcgag	720
	actcctctct aaaaaaaaaa aaaaaaaact cgta	754
40	<210> 36	
	<211> 699	
	<212> DNA	
45	<213> Homo sapiens	
	<220>	
	<221> SITE	
	<222> (483)	
50	<223> n equals a,t,g, or c	
	<400> 36	
	gaattcggca cgagcggcac gagccacctt ctcagtccag tctatgggta tgacagttta	60
	tctgttgaaa acccatcctt gcttctttgt tgccaccag atgcaggtcg cactcataat	120
55	cctccttccc ggactcagga acagcaagac tgttactatg ccattgtccc ctgccctcct	180
	tcccaccttc cttttttttt cctctccac tccttctttt caccctttt tttctgtttt	240
	atgctgttcc aagtattaat tttaaaattg ttctacaaga atgcgattta tcagaaggat	300
	gtgaaccaag cagaatttct tagtatttct ttgccttagg gcattcccct tgtgtggktt	360
	aaaatttgtc cccatttctt ttttgctgtt ggaacttate cttattcttc aagagactcc	420
60	tamtccaat agcactttga atttaacctc cctggtagtt cttctcagcc aaatttcacc	480

	ttnctgaaaa caggattctc tgttctccat gtctggctaa tttttgtatt ttttgtggag	540
	acaaagtctc actatgttgc ccaggcaggt ctcaaacc tggccttaag ccatcctccc	600
	accttggcct cccaagtgc gggattataa gcatgtgcca ctggacccag ccagagaccc	660
	tgtctcttta aaaaaaaaaa aaaaaaaaaa aaactcgta	699
5		
	<210> 37	
	<211> 971	
	<212> DNA	
10	<213> Homo sapiens	
	<400> 37	
	gccaccgagc cgcagttcct gggctcgcgcg gcagctgtga gcgccgaggg caaggcgggtg	60
	cagaccgccca tcctggggcgg cgccatgagc gtgggtgtcgg cctgcgtgct cctgaccag	120
15	tgcctcaggg atctggcgca accccgacgg ggcgccaaga tgtcggacca caggagaggg	180
	ctgaggaact cgcctgcgc cgtgtctgaa ggctgcaccc tgcctatctca ggctttaagg	240
	gagaggtcct cgcaccaggac tttaccgcca gtgaattcca attctgtgaa ttagcacccc	300
	acccccatac ccttctctcc acccccagac taaaggaaga tacttactct ctgcccctct	360
	ccattttatac caaagaaatc ataggtgaaa cccctaccc tcccaacgt taaatgctcg	420
20	agaggaatct tcacaaggc agggccatgc acgcaacctg cacacgcact tggaggggccc	480
	aggtgtctct ccaccagccc ccatgcagta gggactggaa gatatgtcat ctgctggtg	540
	tggtatcact cccacccct accccagccc gtsttcgga atttctcaac taaatttsat	600
	tattgggcag gaaggaggtc atgggttcat ttcatTTTTTg tttttgtgt ttttaattaa	660
	aagaaagggt acctcagttt tcaactctta gacatggatg tagctacctt tttttgtatg	720
25	tctttttttt ttttaagcaat cgtgttgaat taggagtata cttggtgtgg aaagagtatg	780
	aatttgccat gtgatttgca aatgggggga agctactgtg agcgtgtgtt tttttaattt	840
	acactataga gtgatttttt ttcccccaa cgtcaagttt ttaccttgca tgtactggag	900
	tatttatttc atctattaaa atgttatgtt tctcagaaaa aaaaaaaaaa aaaaaaaaaa	960
30	aaaaaactcg a	971
	<210> 38	
	<211> 872	
	<212> DNA	
35	<213> Homo sapiens	
	<220>	
	<221> SITE	
	<222> (2).	
40	<223> n equals a,t,g, or c	
	<400> 38	
	tngcagttct ccacaccgaa gaggacggtg ggcgccaaca gacaggcgat taatgaggct	60
	cttaccaggg caaccaggac tacagtatac attgtggaca ttcaggacat agattctgca	120
45	gctcggggccc gacctcactc ctacctgat gcctactttg tcttcccaa tgggtcagcc	180
	ctgaccyttg atgagctgag tgtgatgac cggaatgatc aggactcgct gatgcagctg	240
	ctgcagctgg ggctgggtgt gctgggctcc caggagagcc aggagtcaga cctgtcgaaa	300
	cagctcatca gtgtcatcat aggattggga gtggctttgc tgctggctct tgtgatcatg	360
	accatggcct tcgtgtgtgt gcggaagagc tacaaccgga agcttcaagc tatgaaggct	420
50	gccaaggagg ccaggaagac agcagcaggg gtgatgccct cagccctgc catcccaggg	480
	actaacatgt acaaacactga gcgagccaac ccatgtctga acctcccaa caaagacctg	540
	ggcttggagt acctctctcc ctccaatgac ytggaactctg tcagcgtcaa ctccctggac	600
	gacaactctg tggatgtgga caagaacagt caggaaatca aggagcacag gccaccacac	660
	acaccaccag agccagatcc agagccccctg agcgtggctc tgttaggacg gcaggcaggc	720
55	gcaagtggac agctggaggg gccatcctac accaacgctg gcctggacac cacggacctg	780
	tgacaggggc cccactctt ctggaccctc tgaagaggcc ctaccacac ctaactgcac	840
	ctgtctccct ggagatgaaa atatatgacg ct	872
60	<210> 39	

<211> 608  
 <212> DNA  
 <213> Homo sapiens

5 <220>  
 <221> SITE  
 <222> (10)  
 <223> n equals a,t,g, or c

10 <220>  
 <221> SITE  
 <222> (16)  
 <223> n equals a,t,g, or c

15 <400> 39  
 ccatacgcan accgcntctc cccgcgcgtt ggccgattct tatggcagct ggcacgacag 60  
 gtttcccgat ggaaagcggg cagtgcgcgc aacgcaatta atgtgagtta gctcactcat 120  
 taggcacccc ggctttacac tttatgcttc cggctcgtat gtkgtgtgga attgtgagcg 180  
 gataacaatt tcacacagga aacagctatg accatgattt acgccaagct cgaaattaac 240  
 20 cctcactaaa gggaacaaaa gctggagctc caccgcggtg cggccgctct agaactagt 300  
 gatcccccg gctgcaggaa ttcggcacga gtttgggtgg agtttccaag gtgaaagt 360  
 ctgaattgg caatcagtga cgcctttgta aagatggctc atgtgggtgg cgctcgcaat 420  
 gaatgcctga taagggcctt tctgtttcct ttgcaactgg taagtgtgct cccatcgct 480  
 ggggaagtta atatcagaca cacacttttt acggtagaag agaggttgac tactccaagg 540  
 25 gcactgaaac tctcactgag ccttattgtt tctctacac cgamttgcag aaagcaggag 600  
 tgctcgta 608

<210> 40  
 30 <211> 855  
 <212> DNA  
 <213> Homo sapiens

<220>  
 35 <221> SITE  
 <222> (850)  
 <223> n equals a,t,g, or c

<220>  
 40 <221> SITE  
 <222> (851)  
 <223> n equals a,t,g, or c

<400> 40  
 45 ctgtaatagc acacaactca gaactcttca gcatttgtgt gattccttac ctctggctga 60  
 taaaactcta atgggtgtg gcttactttg tttccatttt ctttggcttt gtgcaatttt 120  
 tgtgtaactt tacttgtagc tatattttct gtttacagtt ctttttaagg ggaggggtag 180  
 ggttctaaga tcttgttgtt tattgttagt aaaaattttt tcgtgttgta gaaaagcatg 240  
 ggttatgctg ttgactgaaa aagacactgt attatttacc aaaggggtat tgtttttgca 300  
 50 tttgtttata aatgcattat tttggtactg taaatttga cataatttct gagtttatta 360  
 ctactggcat tttctttttc cctttttttt ttttttaacc gtaagtgcac gatgcagggtg 420  
 cataggcccc agaccaaaact agaccaccag catgttcatg tccagacctc ggcagtggcg 480  
 tgcaactgct gtgcacctca gttcctccag tgttgggttg tttgtttttt aattcagcat 540  
 cctgctggtt ttactttcca agcaagatct gttgcgactc ccaaagcgt tttaatgagc 600  
 55 tcacacctat ttgcctttct tcttactgat tttgtgtatt agattgtgca ggagatattc 660  
 tagaaggcat taatgggttg cattcaaaac gatgtggttt gtccaagtta ttttctgtct 720  
 ttattactga gacggattaa tctccttatt tttttcttga tgatttgaag ttgtaacagt 780  
 ttccagcta ttgcttaata aaattttgca gatcaaaaaa aaaaaaaaaa amctcggggg 840  
 gggccccggn nccca 855

60

<210> 41  
 <211> 1042  
 <212> DNA  
 5 <213> Homo sapiens

<400> 41  
 acggcccgtgta attccccgggt cgayccacgc gkccgtgctt cctagaagggt cgtgtcacgt 60  
 ggaacctctt aatctcagca tccggagctc caggaaggga aaatttcaag tcagatagaa 120  
 10 ttctatatat accatttctt tggaaccttc agccctcaag attccaacat catgacctca 180  
 gtttcaacac agttgtcctt agtcctcatg tcaactgctt tgggtgctgcc tgttgtggaa 240  
 gcagtagaag ccggtgatgc aatcgccctt ttgttaggtg tggttctcag cattacaggc 300  
 atttgtgctt gcttgggggt atatgcacga aaaagaaatg gacagatgtg actttgaaag 360  
 gcctactgag tcaaacctca ccctgaaaac ctttgcgctt tagaggctaa acctgagmtt 420  
 15 tgggtgtgtga aagggttccaa gaatcagtaa ataaggaggat ttcacatttt tcattgtttc 480  
 catgaaatgg caacaaacat acatttataa attgaaaaaa aaatgttttc tttacaacaa 540  
 ataatgcaca gaaaaatgca gcctataatt tgctagttag gtagtcaaag aagtaagatg 600  
 gctgaaatth acataagtaa tatttcataa tcttagaatt ctctcaaagc atgtgaaata 660  
 ggaagaaggga agttcttgcc cagaatctta ggaaatcacc actgttcggt tataatcact 720  
 20 gcctcctgaa tcgttgagga gtctttttaa ttagattttt gttttgttgt ctccaagtt 780  
 aatattatat ttagatatca gagagtcagg yaaaaaggaa aacttttatc tctagggaaa 840  
 aaacatttag aaaaatgtat tcagtgtatc taatactgaa atgcggaaaa aaatttaatg 900  
 ttaaaaaaaaa actatagaca ttgacatgga aaagagattt aatgttttga aaaaaaactt 960  
 25 tatattaact gagtaacatc ctctgatga gaagtactat attaaatata aaccattat 1020  
 gttataagtt aaaaaaaaaa tt 1042

<210> 42  
 <211> 702  
 30 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> SITE  
 35 <222> (515)  
 <223> n equals a,t,g, or c

<220>  
 <221> SITE  
 40 <222> (614)  
 <223> n equals a,t,g, or c

<220>  
 <221> SITE  
 45 <222> (673)  
 <223> n equals a,t,g, or c

<220>  
 <221> SITE  
 50 <222> (677)  
 <223> n equals a,t,g, or c

<400> 42  
 55 gggacaatga actccttctg gtctaagtta ttggtgctgc ccctgctggc tccgctgtcc 60  
 atggcccag cctctgcctg tcagagatgg tagagccacc aggacatgga gtcattgctg 120  
 acacagggaa acatgagatg tcttaggttt ggtgtatgtg aaacatgcat gagaaataga 180  
 ggccaaaagt tccactgtgg agcgagaca gaatggtctg aatgctcttg cagtactac 240  
 gtcagtagtt tgtcatctaa tatatattat acatctataa cctatgtatt taccttattg 300  
 tgataaact gttttgtttt gttttttttc taattttgct ttgtgcaaag ccaaaccct 360  
 60 ttcagcagca ttgagctaaa aaaaaaaaaa agtgcattgt tagggctggg cacgggtggc 420



	catgcctata atctcagtag ttcgggaggg cgaggcaggc ggatcacaag gtcaggagtt	480
	cgagaccagc ctggccaata tgggtgaaatc acgtntctac taaaaataca aaaattagct	540
	gggcatgggt gtgggtgcct atagtcccag ctatgcggga ggctgaggca ggaaaaaccg	600
	cttgaaccct ggagcggaa attcccagtt gagccaagat cgcgccactg cactcccagc	660
5	ctgggtgaca gancganact cttgtctcca acaaccagca ac	702
	<210> 43	
	<211> 642	
10	<212> DNA	
	<213> Homo sapiens	
	<220>	
	<221> SITE	
15	<222> (593)	
	<223> n equals a,t,g, or c	
	<400> 43	
	aattcggcac gagcggcggg gtcgactgac ggtaacgggg cagagaggct gttcgcagag	60
20	ctcgggaaga tgaatgccag aggacttggg tctgagctaa aggacagtat tccagttact	120
	gaactttcag caagtggacc ttttgaaagt catgatcttc ttcggaaagg tttttcttgt	180
	gtgaaaaatg aacttttgcc tagtcatccc cttgaattat cagaaaaaaa tttccagctc	240
	aaccaagata aaatgaattt ttccacactg agaaacattc agggctctatt tgctccgcta	300
	aaattacaga tggaattcaa ggcagtgcag caggttcagc gtcttcatt tctttcaagc	360
25	tcaaatcttt cactggatgt tttgaggggt aatgatgaga ctattggatt tgaggatatt	420
	cttaatgatc catcacaag cgaagtcatt ggagagccac acttgatggt ggaatataaa	480
	cttgggtttac tgtaaatagt tgctgttcat ggaaaccgag ggctgcatct tgtttatagt	540
	catctttgta ctgtaatttg atgtacacaa cattaaaagt actgacacct ganaaaaaaa	600
	aaaaaaaaaa aaaaaaaaaa aaagcggccg ccgaattaag cc	642
30		
	<210> 44	
	<211> 1219	
	<212> DNA	
35	<213> Homo sapiens	
	<220>	
	<221> SITE	
	<222> (25)	
40	<223> n equals a,t,g, or c	
	<220>	
	<221> SITE	
	<222> (26)	
45	<223> n equals a,t,g, or c	
	<400> 44	
	aattcccggg tcgacccacg cgtcnnctaa aatccccaaa ctgacaggta aatgtagccc	60
	tcagagctca gcccaaggca gaatctaaat cacactatct tcgagatcat gtataaaaaa	120
50	aaaaaaaaaaga agtcatgtct tggggccaat tataattttt ttcaaagact ttgtcacaaa	180
	actgtctata ttagacattt tggagggacc aggaatgta agacaccaa tccctccakct	240
	cttcagtgtg cctgatgtca cctcatgatt tgctgttact tttttaactc ctgcgccaag	300
	gacagtgggt tctgtgtcca cctttgtgct ttgcgaggcc gagcccaggc atctgctcgc	360
	ctgccacggc tgaccagaga aggtgcttca ggagctctgc cttagacgac gtgttacagt	420
55	atgaacacac agcagaggca ccctcgtatg ttttgaaagt tgccctctga aagggcacag	480
	ttttaaggaa aagaaaaaaga atgtaaaact atactgaccc gttttcagtt ttaaagggtc	540
	gtgagaaact ggctgggtcca atgggattta cagcaacatt ttccattgct gaagtgaggt	600
	agcagctctc ttctgtcagc tgaatgttaa ggatggggaa aaagaatgcc tttaaagttg	660
	ctcttaatcg tatggaagct tgagctatgt gttggaagtg ccctgggtttt aatccataca	720
60	caaagacggt acataatcct acagggtttaa atgtacataa aaatatagtt tggaattctt	780

tgctctactg tttacattgc agattgctat aatttcaagg agtgagatta taaataaaat 840  
 gatgcacttt aggatgtttc ctatttttga aatctgaaca tgaatcattc acatgaccaa 900  
 aaattgtgtt tttttaaaaa tacatgtcta gtctgtcctt taatagctct cttaaataag 960  
 ctatgatatt aatcagatca ttaccagtta gcttttaaag cacatttggt taagactatg 1020  
 5 tttttggaaa aatacgctac agaatttttt ttttaagctac aaataaatga gatgctacta 1080  
 attgttttgg aatctgttgt ttctgccaaa ggtaaattaa ctaaagattt attcaggaat 1140  
 ccccatattga atttgtatga ttcaataaaa gaaaacacca agtaagttat ataaaaataa 1200  
 aaaaaaaaaa aaaactcga 1219

10 <210> 45  
 <211> 437  
 <212> DNA  
 <213> Homo sapiens

15 <220>  
 <221> SITE  
 <222> (422)  
 <223> n equals a,t,g, or c

20 <220>  
 <221> SITE  
 <222> (423)  
 <223> n equals a,t,g, or c

25 <220>  
 <221> SITE  
 <222> (427)  
 <223> n equals a,t,g, or c

30 <220>  
 <221> SITE  
 <222> (437)  
 <223> n equals a,t,g, or c

35 <400> 45  
 gaattcggca cgaggcgccg accaggagag ctggcgcccc ggggctccgc cgcgacccca 60  
 tcgggtagac cacagaagct ccgggaccct tccggcacct ctggacagcc caggatgctg 120  
 ttggccaccc tctcctcct cctccttgga ggcgctcttg cccatccaga ccggattatt 180  
 40 tttccaaatc atgcttgtga ggacccccca gcagtgtctt tagaagtga gggcacctta 240  
 cagaggcccc tggtcggga cagccgcacc tcccctgcc actgcacctg gctcacaaaa 300  
 agagtgaac aaatgcttct attccatagc tacggcattg ctcagtaagt tgaggtcaaa 360  
 aataaaggaa tcatacatct caaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 420  
 annaaanaaa aaaaaan 437

45 <210> 46  
 <211> 533  
 <212> DNA  
 50 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (305)  
 55 <223> n equals a,t,g, or c

<400> 46  
 gaattcggca cgaggaccct atcttacaaa aaagaagaag aagaagaaaa ccatgacagg 60  
 tgtctttaag ctgcccttgc tggtctgggt tcatgaagca tctgtgggag gttgcccata 120  
 60 tgtaaaatta gttgagtttg aagaaatgtt aacgttatat ggtattcttt taattttgtt 180

	ttaaaaataa tttttctcat tcaaatcctg aattagaagt tgtttggtat aaatattgaa	240
	aattgttgag gggagaattt attcaaagtt taatcatttg ctttatctat gttatactta	300
	gctantagtt actggaagtg tcaagtttta tttttagatc ttaactagag tctaaagtaa	360
	ttactaaaag ctagttttca aataatatgt aagagtaaag tcctgagtta aaagatttag	420
5	catactgaat taacttagtt gactgatgct gtacttacat gggcctccta tttcttgagg	480
	ccaagatagc atcaacagaa aaaaaamaaa aaaaaactcg agggggggcc cgg	533
10	<210> 47	
	<211> 1849	
	<212> DNA	
	<213> Homo sapiens	
15	<220>	
	<221> SITE	
	<222> (222)	
	<223> n equals a,t,g, or c	
20	<220>	
	<221> SITE	
	<222> (1300)	
	<223> n equals a,t,g, or c	
25	<400> 47	
	gttttttaaaa aattaaacaa ggctttgtgt tcctagaaga gcttcatttc agtgaatctg	60
	gtgacctcca tctgcttgct gtcataaccc gacacggact tatttttgtc attagcaagg	120
	gggaaaaggc caaaggacaa gggcctcttc tccattgggt tttcctgtgg gcagaagggc	180
	tgaggaagat ggcccagccc gtgggggctg ctgggtcacc ancagygggt aggggtgcaat	240
	ctgggtgtgtg ttccagcagt gagacgggtg tattgtgaag gtggcattca tctgcggacc	300
30	aaaacccagc catcggggaa gggtcagggc ttctgtggaa cttggaacgt gccaggacca	360
	cctgcaaaag ccagggtgctg ttgatcattc tcagatcatt gattggcctc cacttgggta	420
	tgtgaattat tcatgtccca gaagacaaa aagtgtctctg gttctgagat gagtatttta	480
	ttcgtgttct gtttccgaaa cacttagcaa agaaggtcac agtgatgtgg agtcgccga	540
	cccatctttg aagatagcca gtgtccctgg atgaggtgat gatttcccgt cccaaggact	600
35	ctgtgaagtt tagagtacag tttgttgggg tccaaaagac accatctcta cccacccaa	660
	ataaaaatgc actcatctct gtagaacatc tgctgtcaaa ggccagcctg tctgttagggc	720
	atggcttatg cttgacaaac cagtaacaac tgtgggatgg cgatgggtgg atgtgtcgca	780
	agcaattcac tagacaatct tcacatgaat gtcggtagcc agggctcttc ccgagggatg	840
	gctttagtct tgatgaatgt gaaccatgtc ggaattgtta ggtagaaacc tgggctggga	900
40	ggcctcgga cccaggctcc atccctggct tccccagcct gcggccgcaa gcaaaaccaa	960
	gcgcgagatg cagctagcac ccttcatac catccccgtt ctcagcggga caacaccatg	1020
	gacagccgtt ttcagagcct ccagcatttg cacaccacta ctcaccctct ctgctgctgg	1080
	catgttggtg gagtcatccc tgtaatcaag aaatggcctg tggaatgta ttgttcaacg	1140
	ttgtttacag ctcttaaaac atgggtgagga atgcctaagt cttagtgaac aaacgtgacc	1200
45	ttgaaagcag acatagcatg acagaccttc cttagagtgt tggtcgggtt cacagtgacc	1260
	gagagtcagg tccagcacac acctgggaaa gggatgctgn cccaaggggg accaaaaggg	1320
	ccggacgtta cagggtgaaa ccctctgacc cctcgcgaca ccgtaggact tgacttttgt	1380
	ttagtctttc taagaaatag atcatggagc caagtgaagt gcactttgtc aaatgtaagg	1440
	gtctgctttg ttcttgttgc ttttctgttt ttttaacctt tgttccgcca tttaaaaaaa	1500
50	gaaaaaaaaa aagcttatgt ttcttgtcaa atgcagaaat gttccttccg cactcactg	1560
	aagttttgca ttctggcttg tgcagttttt attgtctgtg tcagacgtac agccagacat	1620
	gttctctatt ggcatttttc cgattctgtt cagatgacag cgaccgcctt ttcattcccc	1680
	ccgccacctg tactcacctt cacgctcttt gaagaaaaaa aaaaaaatca ctttgtgtgt	1740
	tgtagctcat ttgtttcaag agagaatcaa cagatcatat tcagtgtctt gaataaattg	1800
55	ctctattttg atattagaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa	1849
60	<210> 48	
	<211> 926	
	<212> DNA	

&lt;213&gt; Homo sapiens

&lt;400&gt; 48

	ctcaaccaca	actagaatttt	gcacaatata	agcttgaaac	gaaattcaaa	agtggtttaa	60
5	atgggagcat	cttggtctgag	aggaaagaac	ccctccgatg	cctaataaag	ttctctagcc	120
	cacatcttct	ggaagcattg	aaatccttag	caccagcggg	tattgcagat	gctccacttt	180
	ctccactgct	cacttgcata	ccaacaaga	gaatgaatta	ttttaaaatt	agagataaat	240
	aagacgtgcg	tggtttctta	agcacagctc	ctccttcttg	atattgcaca	tgcacttcag	300
	ttcatggcta	gctgtatagc	ttccgtctgt	aaacttgat	tttcaagaat	ccttgggtatt	360
10	gaatttttag	aaatgctcac	ataattgttg	ggactgattc	attcctccac	gatatgcctc	420
	ctctctctga	tatcctgcta	actgtagccg	ttgtggcatt	tgagatgaca	ggacatatat	480
	atatatggcc	ccacacttga	ccttgagtgc	ctgaatgctc	tgaaatcaag	catatggcac	540
	agcgtctcaag	acttttgggt	ttgtgtcctt	ttttctatgg	ctgtctcttc	tcaattctgg	600
	agaggtcttg	ttccagtggc	tggtttcyar	ggattgattc	ttaagctctg	gatcacagag	660
15	agaagcaaca	aggaactata	ctcaactcaa	aactttttag	gagaatcatg	aaattgggtct	720
	attcaaagga	tggagttgag	tccatwmtgt	tattgttgca	agaggttgca	tatttgggtga	780
	gtcagttata	aaaaatagtg	ttcttattgt	aaatatgata	cttctcataa	tctattttat	840
	catgtgtata	acattcaaac	tgacaaatat	attgacttat	gaataaagg	gtcaaaaaac	900
20	aaaaaaaaa	aaaaaaaaa	ctcgta				926

&lt;210&gt; 49

&lt;211&gt; 1593

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 49

	gcgagcgcgt	gggctgtgct	ccctgcagtc	aggactctgg	gaccgcaggg	gctcccgagc	60
30	cctgactctg	cagccgaacc	ggcacgggtt	cgtggggacc	caggcttgca	aagtgcaggt	120
	cattttctct	ttctttctcc	ctcttgagtc	cttctgagat	gatggctctg	ggcgagcgg	180
	gagctaccgc	gggtcttctg	gcgatggtag	cggcggtctc	cggcgccac	cctctgctgg	240
	gagtgagcgc	caccttgaac	tcggttctca	attccaacgc	tatcaagaac	ctgccccac	300
	cgctgggcgg	cgctgcgggg	caccagggct	ctgcagtcag	cgccgcgccg	ggaatcctgt	360
	acccgggagg	gaataagtag	cagaccattg	acaactacca	gccgtaccgc	tgcgagagg	420
35	acgaggagtg	cggcactgat	gagtactgcg	ctagctccac	ccgaggagg	gacgcaggcg	480
	tgcaaatctg	tctcgctg	aggaagcgcc	gaaaacgctg	catgcktcam	gctatgtgct	540
	gccccgggaa	ttactgcaaa	aatggaatat	gtgtgtcttc	tgatcaaaat	catttccgag	600
	gagaaattga	ggaaaccatc	actgaaagct	ttggtaatga	tcatagcacc	ttggatgggt	660
	attccagaag	aaccaccttg	tcttcaaaaa	tgtatcacac	caaaggacaa	gaaggttctg	720
40	tttgtctccg	gtcatcagac	tgtgcctcag	gattgtgttg	tgctagacac	ttctgggtcca	780
	agatctgtaa	acctgtcctg	aaagaaggct	aagtgtgtac	caagcatagg	agaaaaggct	840
	ctcatggact	agaaatatc	cagcgttggt	actgtggaga	aggtctgtct	tgccggatac	900
	agaaagatca	ccatcaagcc	agtaattctt	ctaggcttca	cacttgtcag	agacactaaa	960
	ccagctatcc	aaatgcagtg	aactcctttt	atataataga	tgctatgaaa	accttttatg	1020
45	accttcatca	actcaatcct	aaggatatac	aagttctgtg	gtttcagtta	agcattccaa	1080
	taacaccttc	caaaaacctg	gagtgtgaag	gctttgtttc	tttatggaac	tccccgtgga	1140
	ttgcagtaaa	ttactgtatt	gtaaattctc	agtgtggcac	ttacctgtaa	atgcaatgaa	1200
	acttttaatt	atttttctaa	aggtgctgca	ctgcctatct	ttcctcttgt	tatgtaaatt	1260
	tttgtacaca	ttgattgtta	tcttgactga	caaataattc	atattgaact	gaagtaaatc	1320
50	atttcagctt	atagttctta	aaagcataac	ccctttacccc	atttaattct	agagtctaga	1380
	acgcaaggat	ctcttgggaat	gacaaatgat	aggtacctaa	aatgtaacat	gaaaatacta	1440
	gcttattttc	tgaaatgtac	tatcttaatg	cttaaatat	atttcccttt	aggctgtgat	1500
	agtttttgaa	ataaaattta	acatttaata	tcaaaaaaaa	aaaaaaaaa	aaaaaaaaa	1560
55	ctcgaggctg	acggtatcga	taagcttgat	atc			1593

&lt;210&gt; 50

&lt;211&gt; 978

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

	<400> 50	
	gaattcggca cgagatgagt ttggccacgt gatgcaccag ctctgctccc aggtgggtgc	60
	gggcccgggc aggggcaggg gcaggggcag gggcaggggc tgccctgtgt cagcgaggcc	120
5	caagcctggg gcttcggctt ccggctctct ctgcacccgt ccggtggctc cttcatccaa	180
	tgccacccaa agatgggtgac tccctgtcat gcccggtgtcc tggggctgcc ccagcaaaac	240
	accacagacc agggcttaca caagggtgct gtatttcctc atggctcctag aggctggagt	300
	cggaggtcac agtgtcagca gggttggctc cctcgargtc cctccttggc ttgtggccgc	360
	caacaacttc ccgcatctca tgttggtcgtc cttctgtgtg ggtcccaty tygtcttctt	420
10	acrggacccc agtctgccg atccggggccc gcccaacaac ctcaattgac ctagtacct	480
	ccttagacat ctgtctctaa gtagtcacat ctgggattac ggcgtgagcc atgttcccg	540
	ggaatttctt ttttatagta ttggataaag tttggtgttt ttacagagga gaagcaatgg	600
	gtcttagctc tttctctatt atgttatcat cctccctttt ttgtacaata tgttgtttac	660
	ctgaaaaggaa ggtttctatt cgttgggtgt ggacctggac aaagtccaag tctgtggaac	720
15	ttaaaacctt gaaggtctgt cataggactc tggacaatct cacaccttag ctattcccag	780
	ggaacccag ggggcaactg acattgctcc aagatgttct cctgatgtag cttgagatat	840
	aaaggaaagg ccctgcacag gtggctgttt cttgtctgtt atgtcagagg aacagtcctg	900
	ttcagaaagg ggctcttctg agcagaaatg gctaataaac tttgtgctga tctggaaaaa	960
20	aaaaaaaaaa aaactcga	978
	<210> 51	
	<211> 433	
	<212> DNA	
25	<213> Homo sapiens	
	<220>	
	<221> SITE	
	<222> (424)	
30	<223> n equals a,t,g, or c	
	<220>	
	<221> SITE	
	<222> (430)	
35	<223> n equals a,t,g, or c	
	<220>	
	<221> SITE	
	<222> (431)	
40	<223> n equals a,t,g, or c	
	<400> 51	
	cggccgctct agaactagt gatcccccg gctgcaggaa ttcggcacga ggcgggaagg	60
	cttattccaa ggtaagagg gctgtgtgaa ggggcagtgg gatggaatgg ggggtggcat	120
45	gggacaggca caagggaagc ctccagcccc ttttctgcca caagcaagag gcactcagcc	180
	ctacctgaga tgtgttattt tttagaaata tctttattga tggctcttgc actcaatata	240
	aaggcagcat atgggtgttg caatataaat ggtacagaag tccacagagc aaaagggccca	300
	gtttctgtcc cctttcctct ctccaggcct ctttctggga cccattatt ggatagatta	360
	agacctttcc agaccttgta aaaaaaaaaa aaaaaaactc ggggggggsc ccggaaacca	420
50	attngcccn naa	433
	<210> 52	
	<211> 861	
	<212> DNA	
55	<213> Homo sapiens	
	<400> 52	
	gaattcggca cgagcctgag tcaacttgat atccaagctt tttacttcaa ttatctggca	60
60	agattacata gactgtcaaa gtttgtgaaa gtttagcaag aaaactgtct tactcacaga	120

	accacaggac taactgactg aaccacactc caccatttgc ccctatttcc aggcgttatg	180
	gtcacccctgt agtttctaat ctgtatagat gtgtagagca tgcctcttcc ctcttccttt	240
	ccccccctg ttttccttcc ctcttgccct ttcttaatgt ctgtytctat tggcttcttg	300
	atcttggctc ttaatgttca tccttaagct tgcttctctc ttcagactac tgattcagcc	360
5	tcttgcatatt tctttcaact tgggccaaaa aaacaggcaa cattttcttc ctccactacc	420
	tcacatcatcat ccaattttatt cctttagttt atattaccac aactctccta aacgtcccaa	480
	gtctatttatt aagtctaaca acttagcttc gaacctcaat ccaagcatct gacaacacac	540
	tgaaatgtgc aagcaagagt ccwattggcc ggggtgcagt gctcatgcct gtaatcccag	600
	cactttggga ggccaagggt ggatcacctg aggtcgggag ttcgggacca gcctggccag	660
10	tatgggtgaag ccattgctmw actaaaaata caaaattagc cggacattgt ggtgcacgtc	720
	tgtcatccca gcaaggcagg cgaatcgctt gaacccggga ggaggaggtt gcggtgagcc	780
	gggatcgtgc cattgcactc cagcctggtc aacagagcga gactccgcct cattaataaaa	840
	aaaaaaaaa aaaactcgta g	861
15	<210> 53	
	<211> 510	
	<212> DNA	
	<213> Homo sapiens	
20	<220>	
	<221> SITE	
	<222> (380)	
	<223> n equals a,t,g, or c	
25	<220>	
	<221> SITE	
	<222> (396)	
	<223> n equals a,t,g, or c	
30	<400> 53	
	gatcccccg gctgcaggaa ttccgcacga gtgaaaaccg cctccaccaa ccccccggt	60
	tgccctacacc accccccttt tacttagtat gtttattttt tgtgtgtctc ttgccttctc	120
	cccacgtttt atttcccctc agagctgtga atgggcagggt ctgtctctgg tttggcatca	180
35	ctgagttttt cccatgcatt ggccccagggt ctgctaggat gtgagacaaa tctccctaca	240
	atgggcttgc tcccattgtc tgtacagttt aatagatgct ggcattgtcg aggttaccca	300
	tgagtcaaaa tccgctctcc atgcttactc ttgacacccc attgaagcca ctcatgtgt	360
	gtgcgtctgg gtgtgaagtn ccagctccgt gtggtnccctg tgcttgact gyccctgctt	420
	tgcagttcct ttgcacttac tcatcgagtg ctgttttgaa atgctgacat tatataaacg	480
40	taaaagaaaa aaaaaaaaaa aaaactcgta	510
	<210> 54	
	<211> 309	
45	<212> DNA	
	<213> Homo sapiens	
	<220>	
	<221> SITE	
50	<222> (301)	
	<223> n equals a,t,g, or c	
	<220>	
	<221> SITE	
55	<222> (305)	
	<223> n equals a,t,g, or c	
	<400> 54	
	gaattccccg ggataaattt catttcccaa agatgagtag gtatgaaaaa taatactcag	60
60	aagagattgt tcttgtgggg agaactgctt ctacaggatc tagctttgat tttgtatctt	120

	tcaatctttt taaatcaac tttacgaat ttaaacctat ttttaagtgt caagtaataa	180
	gtttgacaat tgtatgtgac ttctaccaca ataaaatata gaacattttt atcattctat	240
	aaaaaaaaa aaaaaaaac tcgagggggg gcccggtacc caattcgccc tatagtga	300
5	ngtancgtc	309
	<210> 55	
	<211> 1585	
	<212> DNA	
10	<213> Homo sapiens	
	<400> 55	
	ggaatttctt aaatatgttc atgtataata cttgatcaaa atatttttgg gttttttggt	60
	ttgttttaat gggtttagaaa atgtttacaa tcttggtctt atatgacac caatggaata	120
15	gtaacttcca ggtttatata aatatgagct gactttaact gagttgtttg ggataggaa	180
	gaagcagtc cttacagta tacaactact gcttgccagc tggatcaaaa taatcatgtt	240
	ttatgaaaat atctccctta agcagtggtta aggttggttt gcagtgtgta agtggcacat	300
	tgaactggaa gttttcttga aagctgcttc atctattaag aagcaatttt caaattgtag	360
	cgaattatat tatccctctt tttaaagaaa cagtcgttat atgctgatgt ttcttaaaat	420
20	aactaaaatg tkcctcttaa tgtgatttta aatggagttt tttgtaggtc ctttcttagt	480
	agtaaagaat cttcttagagg gaaacatttg tgcttttagg gataatcttc cttgtgcctc	540
	actacatccc taagtgggta tgactcttgt tattaccaca tgctttttta gtatatttca	600
	caaattttact tttaaatatt attttagata cgggtgtaaca tgtgcaattc agaataattt	660
	tataacaggt catgaaaaac ataactttag ttaggattca caatatttgt wctccacata	720
25	atgagagaat gaatgagcct ttggagatac tgatataagg caattatttt ttgcaatgtt	780
	gaatgtgttt tttagtttga ttcttttttt tcccccaat agggcactac ctgccatata	840
	atcttgtatt actttttgat gtaaagcgac taatatttac actatgccat atttttttta	900
	attatagttg taaattatga aagatccttg aattttctac agatctacaa ctactaatgt	960
	aacagacaag ggcaatcttg gtatttaaat ctgagcatgg cagttctacc ataaaaagta	1020
30	ctctattttt ctaatttcta ggatttttaa aataacattt ctgtaagtct gacatactaa	1080
	tagtcactca agcagtagca tttatttttag tttgcatata ttttactgt ttttaattta	1140
	atgtattgag tctaatagga ctgttttgca ataattgaa taaagattta tttcttctaa	1200
	tcaaagatgc ataacagcta ttatctaggg gaccmccaaa tgtgatttca aaattttgtt	1260
	aactattaca aatgtaatcc ttatatagaa attttaattt tgtaaagtag tgtataatat	1320
35	tgtaattatt aattcttggt cttaaattca aatatgtatt gatcttcaat gtgctgtgtt	1380
	aaatcttgct tctctgaaaa gttggagaca agatttgtct tcctttttac agtttgtaat	1440
	tttactgttt ttattcctgt taaaaaaaaa aaaaagtcatt ttgtaaccca tgcagaccat	1500
	tgtttgatct atgctaactt atcaacttgg ctattcaata aagttaattg aaaagaaaaa	1560
40	aaaaaaaaa aaaaaaaaaa ctgca	1585
	<210> 56	
	<211> 874	
	<212> DNA	
45	<213> Homo sapiens	
	<220>	
	<221> SITE	
	<222> (468)	
50	<223> n equals a,t,g, or c	
	<220>	
	<221> SITE	
	<222> (501)	
55	<223> n equals a,t,g, or c	
	<220>	
	<221> SITE	
	<222> (546)	
60	<223> n equals a,t,g, or c	

	<400> 56	
	aggggaatct cggtgctgcg acgagtgtgg ggccagccgt ggaggctcca ggtgttctct	60
	ctgccccagc agagcccgcc aggagcccca acaggaagcc agcgcgccat ggctgccacc	120
5	gacttcgtgc aggagatgcg cgccgtgggc gagaggctgc tgctcaagct gcagagactg	180
	ccccaggctg agcccggtga gatcgtggcc ttctcagtca tcatcctttt cacagctact	240
	gttctgctgt tgctgctgat agcctgcagc tgctgctgca ctactgctg ctgccctgag	300
	cggagaggca ggaaggtcca ggtgcagccg acaccacccat gacggacggg cgatggctga	360
	ggagaagctg gagaggagat ggccaatgcc atgacacagg ccacagccct ggccctgcag	420
10	cccttaccct tcaagaccag gctccccctg cccagctct ggcccagncc caggtacctg	480
	gacactgaca acttgagccc ntaccaagga aacaagggct ggtatagggtg caaacctctc	540
	atctgncagc tggacactgg gtgctgggga gtcagctgtt tcaaagactg ggtcaactgc	600
	ctgggcttct tcgctacct gcacttttta acaaaacaag gaagtagggg tccccatacc	660
	ttgatggaga acagtcccca cctgtgggca attggccctt ggggctctgc tgatacatgc	720
15	caaagaggag caaggcaatc agaggggctt tgtgcaatag cttctgcacg cgagctcccc	780
	ccagagcgtg agcatgtcag tattctagtc cagtatttgc cagtttccaa gtaaaagctt	840
	ttgtgttaaa aaaaaaaaaa aaaaaaaact cgta	874
20	<210> 57	
	<211> 1169	
	<212> DNA	
	<213> Homo sapiens	
25	<220>	
	<221> SITE	
	<222> (2)	
	<223> n equals a,t,g, or c	
30	<220>	
	<221> SITE	
	<222> (9)	
	<223> n equals a,t,g, or c	
35	<400> 57	
	gngcgccnc cctttttttt tttttttata ttttatcaat tttattgaaa tattccaagg	60
	atcccaaccc catttaaaaa taaaaattgt aaagcactcc attcaataaa agcacataag	120
	tccccctcaa taattagtat gacaattcac gatacagctc ttactctggg agagtttatt	180
	ttacccttta ttccaaaagg caciaaagtc tctgaggcct cagatattaa cccactgca	240
40	tgtaaatgac acaccactga ggtgcagctc aatgtaatta ttaaagctta taacacactt	300
	ccccaagaat ttatagattc ttctataaaa taataattta aaaaatactg caccttaaga	360
	ccaatacagg cttaacaaaa gacctgaaat ttctgcaagg gcagttttgt ttcttgatag	420
	aagtacaact ttgaaagtc tattccagc aaaagaaaca ctagaccag cttggccaaa	480
	gaaacaaaat aaaacaagt atttctaaca cgctaaaaga gtacattttc atcagctcca	540
45	aagaaagcag tcttggtcat tcagaaggct cctatgatcc caccagtctg cagtcattag	600
	aaatatatgc ttacaggcc acaggctgct ctggatttgg ttccagacac cagtgaccag	660
	aagaagccag ttttgcgtgt gaggggtgtg ggcccccgct gccttgggccc tgctcaccgg	720
	ggtggatgga cccccgcgg gtcacagcct gctgtcacgt ctggactgtt ggcctcttct	780
	gcactctggc tggtgggctc tctgtctctc tgtccctcag tcacgtcatt gtctggctgt	840
50	ccggtgctgg ctgcactctc atttgtgagg ataaccctt ccttcttctt ttctcccaat	900
	acctccagcc ccacatcctc gagataatga agccgttcat tcttgggcac aaaagttcga	960
	atggaggcct ttccccgcca tccgcataag acgatgggac actgcagagc gtctggattc	1020
	gcagaatctg gtccatactt cagcacgatg cttccctttg ccaggctcct tgcttgactg	1080
	taggtctcac tgetgagttt tctaaaaaag ggattttcct gggtaacag tatcttaaca	1140
55	tcttccattg atacagtaac aattctttg	1169
	<210> 58	
	<211> 1066	
60	<212> DNA	



&lt;213&gt; Homo sapiens

&lt;400&gt; 58

	gaattcggca	cgagcaaatg	ttgaaccaat	tatgttttgg	tggtgggtgtt	cttagctgtt	60
5	gaatcctgaa	tggtttataa	agtgaactag	ctggcctaata	gcagccagcg	ttctgggcag	120
	cagaacatat	tcattccttac	tgtaaatctt	atttgctgct	tccaaagggtg	atgattttca	180
	agcagacatg	ttctatatgg	tctgtgtttt	aggatctggt	gcccagcctc	tatcagagct	240
	tgccctacctg	gcaaagctgc	ctacccttca	agtgggaaaa	tataatccac	tgtttaacaa	300
	ggctcaccct	ctccaccctg	tcctaacgac	cttttggtgaa	tggtgctgtga	tattttcttg	360
10	ctcaaatagca	aggtggtagc	tctgctttca	ttttaagaaa	gtggaggctg	agggcattgt	420
	atcaatactg	ttgcaactcc	aagaagtttt	ccttgtaaaa	ttaaaggaaa	gatcttgtaa	480
	ttgattaacc	atcttcttat	gccttgctat	tgacatatct	atgctctttc	tacgtctagt	540
	ggctgaaaat	gtttgcattt	gttcatttga	ctaattgggt	gattttttgky	ycwatattat	600
	tagacctgta	atgtttttaa	atgtatttta	ttaaatgttg	actggatgta	tgkcctctag	660
15	caatacagg	tactttctaa	actattaagg	gaggggttgt	aycctcatgt	tgagataaga	720
	tgatggctgt	ttaaattttg	caattttttt	tgccctgcag	ggatattttg	tgtttatgtg	780
	tccaaaaaag	gaataaatg	gcattcttgt	gccaaaagtt	gtttttctctg	tcaattgtct	840
	aataagtatg	cagtacactg	taatggcaac	atacatggtt	gctttataaa	aacagtttcc	900
	tcagtatgag	aaattttaca	aagaacagtg	gaaaaacttt	gtgtttttaa	ctcttgggtc	960
20	tccttatttt	taaaaattgc	tatttggtat	acaattatta	tggtgtcaatt	aaaactaaaa	1020
	taaaactttt	aaaaaaraaa	aaaaaaaaaa	aaaaaaaaaa	ctcgta		1066

&lt;210&gt; 59

25 &lt;211&gt; 772

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 59

30	gaattcggca	cgagctttcc	tgagcctcag	tttctccaac	ggtgggaggt	ggtagaaatt	60
	gatatagtac	ttaccactga	gggtaaaatg	agatataacc	tggtgaaata	ctgtacacca	120
	cagtcattca	atagtggcag	cttaaaaaaa	ttattctacg	attacccttg	cttcagtgat	180
	tcttcttggt	gttattgaag	ggtgagatct	cggtggggat	ctcccaggtg	tttccataat	240
	cccagcgatc	accccaggga	gaacctctct	ccttaggctg	ctagaggaca	tgtgccatag	300
35	gaccagatag	gagggagggg	cagcgggtgg	aatgcgtttt	cagagctacc	tttggccaag	360
	ccgtatcctt	gtggggacct	attgcattgc	tgctgaagtg	ctgttcccat	cagccctggc	420
	ttcgtgtggc	cctgtctggc	aaggggggtg	tcctacaaag	tcatggcagc	ctggtgccaa	480
	aaccatcatc	ccataggacc	tgctgtagct	ttgccagaag	cctggcccaa	ggggtggagg	540
	cccctggagc	tctgaccac	cacgtggagg	gtgggaaatg	ccacagagca	ggttctctag	600
40	aagggatttg	tcagaagcta	aactgggggtg	ccccctgggc	tcaggcctgc	acagtttctc	660
	cctgaccacc	cagctgggat	ggatatagag	acagggtgtca	tggtgcagaa	agcctgccct	720
	aagaggccct	actggtgttt	tcctttatta	aaaaaaaaaa	aaaaaaactc	ga	772

45 &lt;210&gt; 60

&lt;211&gt; 1198

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

50 &lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (1189)

&lt;223&gt; n equals a,t,g, or c

55 &lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (1191)

&lt;223&gt; n equals a,t,g, or c

60 &lt;400&gt; 60

	tcgacccacg	cgctccgattt	aattcttatt	ccccacagtt	taggtatttt	tcattagtag	60
	atcaatttga	cacactgaat	gcaagactat	taaggaagaa	cgattaaata	ttattttatt	120
	ttgtgaagag	ttggcagcag	attacatctc	aagaacttgc	agagagagga	aggtagatgg	180
	acaatcctaa	attgtaagat	gttacaacaaa	acagtgaagt	aagagtactc	ctgaagacta	240
5	aaatagagag	gctgggggttt	gagccatttt	actgagtagc	ttagctggaa	cctgatataca	300
	gaagtgcct	ttaacacaaa	gcctcttggc	aattgtatgg	tactaacaac	tagagtactg	360
	aagtgtgaagt	tgaaaccaag	ttgcagtggg	aaatcaaagg	tgaggtagct	tatttgaaac	420
	cagcaaatga	gacagggttg	acagttttta	aatctcttct	aacaaagaaa	ctgcacggta	480
	gcaaggacta	gcggttctca	aagcccttct	ttttcagtgt	tctcattcac	cttggcacc	540
10	aagtatgttt	aacaggccat	gcattaaaaa	taaatacaaa	aataataaaag	ccgcttaaag	600
	ggaacttaca	aactgacaat	ctctcctctg	tatttgtgtt	catagtggct	gggagttaa	660
	ttatatgcac	aaaagttagg	agccacttgt	ttctgcacag	actgtaggag	caagatgagg	720
	agatggcgag	gttttggtaa	gagccccag	ttctggtgga	caggcatact	tgtggcattg	780
	ggtgcggcat	tgtctggagg	accacgtctt	gggaggcgat	tgacttttgg	tttgaatttt	840
15	ccctttaaac	aagaagagat	ggctcacatt	ttccatatat	atctcaatga	atgtactgta	900
	ttactgtttt	aaaaatttga	tgaataata	atgaattggt	ctccttttgt	tatctggtcc	960
	ttgtttaatt	tgtttaaggg	tttttgtata	caaaagttaa	catttttatg	tatatattttc	1020
	ttgtgtaaaa	actgtatgta	tatgtgtatg	aaacactgta	tgtattatct	gtatatagtg	1080
	tgacaaaaatc	atttttcttt	cttctctttt	gaagatttaa	taaatcttgc	tgtgaagtaa	1140
20	aaaaaaaaa	aaaaaaactc	gagggggggc	ccggtaccca	ataacctnt	natgatct	1198

&lt;210&gt; 61

&lt;211&gt; 558

25 &lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 61

	ctgcaggaat	tcagcacgag	ytggcatgtg	acaaccag	gctgcctgaa	aatggatacc	60
30	aaatcctgta	caagcgactc	tacctgccag	gagagtcctc	caccttcacg	tgctacgaag	120
	gcttttagct	catgggtgaa	gtgaccatcc	gctgcaccc	gggacagcca	tccactgga	180
	acggggccct	gcccgtgtgt	aaagtagcag	aagcggcagc	agagacgtcg	ctggaagggg	240
	ggaacatggc	cctggctatc	ttcatccgg	tcctcatcat	ctccttactg	ctgggaggag	300
	cctacattta	catcacaaga	tgtcgtact	attccaacct	ccgcctgcct	ctgatgtact	360
35	cccacccta	cagccagatc	accgtggaaa	ccgagtttga	caacccatt	tacgagacag	420
	gggaaaccag	agagtatgag	gtttctatct	aaagagagct	acacttgaga	aggggacttg	480
	tgaactcaac	cacaatctcc	tcgagggggg	gccggtaccc	aattcgscct	atagttagtc	540
	gtattacaat	taatgggc					558

40

&lt;210&gt; 62

&lt;211&gt; 616

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

45

&lt;400&gt; 62

	gaattcggca	cgagtcttga	cagcctggtc	accaagggtt	tggaaaaagg	ttctattgga	60
	gtggagattg	atgggtggaa	aaaggagaga	ggggagttgg	acctgatacc	aaagagatgt	120
	tttcagccat	caaccagctg	caaaacaaga	tgggcttctc	tttctacat	attcttccaa	180
50	gcatcataaa	tactcgggtc	gtcccccaac	ccacatcctg	caggatgcag	ccagagcaac	240
	agccccactc	cactctgaaa	ccagtcaccc	tagggatgat	gatcatttct	tagcttccct	300
	gttgagggtc	ggttgggggt	ggctgatcgc	tgcttgggtc	actcctgcac	tggctgggcg	360
	ttggctgcat	ggttaaagctg	ttccctgtct	catcctgttg	ggataaacag	agtatcctag	420
	gcatattttc	tccagagcag	tggcagacac	aaagggtcaa	cagaaacctc	caagggtttg	480
55	tcatgcctac	tcttgcaact	agcacattgt	catttcagcc	tcatgctatt	gaccaaagca	540
	agtcacttga	ccaaattcaa	agccacaaaa	ctcgtgccga	attcgatata	aagcttatcg	600
	ataccgtcga	cctcga					616

60

&lt;210&gt; 63

<211> 811  
 <212> DNA  
 <213> Homo sapiens

5 <400> 63  
 gaattcggca cgaggagctt ccatcttttc tgatgtgagt ggtgtcagga atgactatgg 60  
 tgggtggtagt ggcagtggtg atggttttct ggaggctgaa aggttaaagt cccaatgcag 120  
 aagtgatgtc agggcttagtg ggtggcggta gcagggtcag taaagtcagg ttcagatgct 180  
 tcaatgggta ctccctttctc gtgttagtcc tacagcatca tttcagactt tgttcttggt 240  
 10 gcttagctcc aagcctcttc ctctgctgt cctgtcaggt tgtgtccact atgatggagc 300  
 aagaccctgt catctatgat gatgatgacg acttgcctaa ttatttttct gtttaagcta 360  
 gccatagtgg atcctgttat ttgtgcctaa gagctcttac tgacaaagaa cgtgttaccg 420  
 gaagtgggat gctacaagta acaacactaa aagtagaatt gactaagtgc agcaggcagg 480  
 cctttgagca aggaggggac acacattaca ggctggaag ctggtgactc ttgtaatgca 540  
 15 gtggcaaaat tttgcttcaa ctactatata caatacttga agatgcacac tgcaagctga 600  
 gtgaggctgt gataagaggg gaaatagtgg ggagcattca gaatgttggg ttacattgat 660  
 gacttcttgc tctttcagca gtcttgatag agcagctata cccacaccag agtcctccag 720  
 ctgacaagag aggttaaggag agaaactgct ttgccaggag gggccctctg ctgcagctgg 780  
 aggtccaagt tgaccgagag cccaaatttt g 811

20  
 <210> 64  
 <211> 993  
 <212> DNA  
 25 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (370)  
 30 <223> n equals a,t,g, or c

<400> 64  
 ggcacgagcc caaagtgctg ggattacagg gagttgatga aagtggagat gtttttagag 60  
 ctacctatgc agcattcaga tgttctccta tttctggtct gctggaaagc catgggatcc 120  
 35 aaaaagtctc catcacattt ttccccagag gtagggggga ttatccccag ttttgggatg 180  
 ttgaatgtca cctctttaag gagcctcaca tgaaacacac gttgagattc caactctctg 240  
 gacaaagcat cgaagcagaa aatgagcctg aaaacgcatt cctttccacg gattccctca 300  
 ttaaaataga tcatttagtt aagccccgaa gacaagctgt gtcagargct tctgctcgca 360  
 tacctgacan gcagcttgat gtgactgctc gtggagttaa tgccccagag gatgtgtaca 420  
 40 ggttctctgcc gactagtgtg ggggaatcac ggacacttaa agtcaatctg cgaaataatt 480  
 cttttattac aactcactg aagtttttga gtcccagaga gccattctat gtcaaacatt 540  
 ccaagtactc tttgagagcc cagcattaac atcaacatgc cctgagctt caaacccaag 600  
 tcccgaggc aaatttgaag ctttgcttgt cattcaaaca gatgaaggca agagtattgc 660  
 tattcgacta attggtgaag ctcttgaaa aaattaacta gaatacattt ttgtgtaaag 720  
 45 taaattacat aagttgtatt ttgttaactt tatctttcta cactacaatt atgcytttgt 780  
 atatataatt tgtatgatgg atatctataa ttgtagattt tgtttttaca agctaatact 840  
 gaagactcga ctgaaatatt atgtatctag cccatagtat tgtacttaac ttttacaggt 900  
 gagaagagag ttctgtgttt gcattgatta tgatattctg aataaatatg gaatatattt 960  
 taaaaaaaaa aaaaaaaaaa aaaaaaaaaa att 993

50  
 <210> 65  
 <211> 689  
 <212> DNA  
 55 <213> Homo sapiens

<400> 65  
 gaattcggca cgagctaagg tgggcgggtc acttaagcct cgaactcctg gcctcaagca 60  
 atcctcctgc ctttccctcc caaagctatg aaattgcaga caggagccac catgcctggc 120  
 60 tgggttttgg gggccatggc aagtgcaggc ttgtcagagg aattggagaa gcagggatta 180

	gtaggaaaa cctctccact tcttgtgttt catgccaggt agtgtttgta acttcagaac	240
	ccgcccttac cttacctacc taccatgtta tgctcatttc acctactgtc cctgctgta	300
	tagggagtgc cttgagggca gagatcatgt tagttttgtt cctcttctg tacagagggt	360
	ggagcccagt acctggcaca gctgaaggag gaatgtgctg ctgctgtctc tgtatttcca	420
5	ggtactcctt gttgacctct agccaagaca aggaacctcc ttatgagatg tcatcttctg	480
	agctctcttg atggagggaa taccacggtg atgattgaat atgaaaagtc ttggcacagt	540
	ggctcacacc tgtaatccca acactttggg tggccgaggt gggaggattg cttgaagcca	600
	ggcattgaga ccatccttgg ccaccaaacg agaccccatc tctacaaaaa aagaaaaaca	660
	aaaccaaaaa aaaaaaaaaa aaactcgt	689
10		
	<210> 66	
	<211> 942	
	<212> DNA	
15	<213> Homo sapiens	
	<400> 66	
	gaattccagg actgctggga ccccttcgac ctctctggcca cggagagatc ctgctcccag	60
	ggaccagcgt ctgggtggga cacagttcac tctctctctc acttcatgtt ctttttcttc	120
20	agcagatggc tcaagttcct tgtttttctc ctgctttctt gacagccgta gcttctgaaa	180
	cctgccattt ttggtctcct gatgcctgat ttcttaattg tctgactgt gtcttctagg	240
	aagcattaag tctgaactga cttattaggg aacttcagaa agttaaacac acaaaaccct	300
	ttctttgact cctatcttaa ggacatggag atacagttac atatatttat acacaaggat	360
	attcatatgg caaaaacggg gagaaggcac aatttaagag cccaatgggg actgggattg	420
25	tgtatgcatc tgtacaatga catgttatga agtcattctg tttttataa aactttttag	480
	tgacatggga aaatacaaaag aatgtaaaga atttaaaaag cagcgtacaa aacmatatat	540
	gtgatccaat ttgtgggtgga aatattttat ctatatatat ccatttttaa mcaccaarga	600
	aaatacacag ttaacagtag ttatcttttg aaggcaggat tataagtgat cttagttttc	660
	ttccttcac ttttgttacc gatatcagaa aaaaactctg tctctacgaa aataaaataa	720
30	aatgaaataa aataaaatta gctgggtgca gtggctcatg cctgttgctt cagctcctca	780
	ggaggctgag gcgggagaat cacttgggcc cggcaggctg aggctgcagt gagctaggat	840
	cgtgccactg cactctagcc tgggtggcag caagacctg tctcaaaaaa aaaaaaaaaa	900
	aaaggaattc gatatcaagc ttatcgatac cgtcgacctc ga	942
35		
	<210> 67	
	<211> 2309	
	<212> DNA	
	<213> Homo sapiens	
40		
	<220>	
	<221> SITE	
	<222> (13)	
	<223> n equals a,t,g, or c	
45		
	<220>	
	<221> SITE	
	<222> (652)	
	<223> n equals a,t,g, or c	
50		
	<220>	
	<221> SITE	
	<222> (677)	
	<223> n equals a,t,g, or c	
55		
	<400> 67	
	ggtaagagag aangtgtgaa gtcacctgtc tgttctagtc attccaatgg acattgtact	60
	ggcccaggag gaagaacca gatgtggttg tccagtcac caaagcaagt ctctagcaca	120
	aagcccgttc cactgaactg ccttctcca gtgcctctc tgtatttga tgatgatgga	180
60	ctcccccttc ccacggatgt gatccagcat aggttacggc aaatcgaagc aggtacaaa	240

	caagagggtgg	agcagctacg	tcgacaggtg	cgtgasttca	gatgaggctg	gacatccgtc	300
	actgctgtgc	ccctccagca	gagcccccca	tggactatga	ggatgatttt	acatgtttga	360
	aggagtcaga	tggcagtgat	actgaggatt	ttggctctga	tcacagtga	gactgccttt	420
	cagaagcaag	ctgggaacct	gttgataaga	aagagactga	ggtgactcgc	tgggttccag	480
5	accatattggc	atcacactgc	tataactgtg	actgtgaatt	ctgggtggcc	aaacgaagac	540
	accattgcag	aaattgtggg	aattgtatttt	gtgctggatg	ctgccacctg	aagctgcccc	600
	ttcctgatca	gcaactctat	gacccagttc	tcgtctgtaa	ctcatgttac	gnaacacatt	660
	caagtctctc	gtgccanggg	aactcatgag	ccaacagctg	aagaaaccca	ttgctacagc	720
	ttccagttga	atgccgggga	gaaacctgtc	caatttttagc	aggtttgaag	ggaggatctt	780
10	cttcagttgt	agtttgggaag	gttccttggg	gtggctcatg	aaatcacaga	gctcagagat	840
	accatcttga	gaaatcctcc	ttggtatcat	gaaactggag	cagagggaatt	gcaatttagc	900
	aggaggtcct	ctactggtga	tacctcacc	ttggggtaat	ggtcctaacc	cagacccagg	960
	gtctggaaag	cttaattgtt	agttggtgac	tccagcctct	ttctcctgga	ggtcacaaga	1020
	tgatgattgc	gtagatgttg	cctggtgcaa	agtgcctcaa	acagcaatag	aaaggcata	1080
15	gtataaccaa	aatccaagt	ataaccagac	ccatctctcc	tccaccttga	caaaagcaga	1140
	ttatagtata	caaggtagga	attcctgtcc	tatttgagat	gaactatata	ctgtacctct	1200
	gtgctctgtg	tctgcatgaa	ggctcagcct	ttagaggcac	tccttctagt	tgcattagta	1260
	ctgtctttct	gtggagtttg	gtttgaagac	tggctcagca	agtggagggt	tcaatgtatt	1320
	tttcagttgg	ctcatcagcc	agcattggtg	aattattcagt	ttaggggaac	agttctaggg	1380
20	agtggagacat	ttttgggagc	agaggaaaac	tctgctgatg	ttcggctcctg	gcaaaccattg	1440
	agttattttg	agctgtgaag	gcagtcgtct	ctgttacaca	gtggcagctc	ttgagttatg	1500
	cactgtgaag	aatgagaagg	gaaaagcaaa	aattatcctt	gtgaaatata	tgctgattgt	1560
	gccctactct	ttgcacctga	cttttcctag	ttgtcctggg	gctaacacag	gagctacacc	1620
	ttgatcctct	cctggcatga	aaataaaaca	aagggttttcg	ttgttggtgt	tccattgccc	1680
25	atttccccca	tggtgtcttt	cccttggtcg	atgcctcctc	tgggtcacat	tgcttcttat	1740
	cctgaacact	tgacaccttg	agggtagaat	ttagcgtttg	gtttttacct	cctagcatat	1800
	gctgttttgt	atgtgagggt	ttcagtacaa	atgctgctgt	ctatttctgt	gcacttaaca	1860
	atggaaccca	aacagaagag	aataaagcct	tgataccaaa	attgggaaag	aacatgtgtc	1920
	catttggacc	aaacgttggt	ggttttttaa	aaattttatt	ttgttttttt	gtttttgttt	1980
30	ttgttttttt	tcatcttaat	atgtaccagt	ggcacttaac	caaaagatac	agtgatatag	2040
	ccatgtatct	gtctacttag	cgtggctgtt	ttgagggact	gtcccatcag	tgaacaaact	2100
	gcatggcctt	ggagagagac	tctgggctct	tggctcagat	gtgttcatca	aatactcctt	2160
	tcagagctgt	tgtgggtgta	agtgacatga	tgtggccaaa	aatccaaact	gtgcagttgc	2220
	gttgtgacaa	acatgcaatg	tgctgtaaaa	attcaatata	gtttaataa	aatctctata	2280
35	ttagtaaaaa	aaaaaaaaaa	aaactcgag				2309
	<210> 68						
	<211> 814						
40	<212> DNA						
	<213> Homo sapiens						
	<220>						
	<221> SITE						
45	<222> (421)						
	<223> n equals a,t,g, or c						
	<400> 68						
	tacgagtttt	tttttttttt	tttagccata	attacacaaa	acattagtgc	aggacaccat	60
50	tttaaaaaaac	tattttaa	agtcttcaga	gaaaaaatat	taagtattac	agtttaggag	120
	tatattgact	ttggggccaa	ggattccaat	attttacaaa	aaggcaatat	ccacgcaaca	180
	tattccagat	tcgggtgttg	gagaagctgc	agggcttgag	gtgactctat	cacaactgct	240
	ttccgtacgg	aggagccact	gccaaactgtg	tggacgagaa	tacttaagca	cgtgcttcat	300
	tgetccactg	ccacaggtgg	atatttcagg	ggaattatta	ttaatttcaa	agttttttta	360
55	aaargytatg	ataagtaa	aaaagtaatg	gtaggaktca	cggtcggaga	gcttatcgcc	420
	naagtctttc	tatagccttc	ccccggaagc	cccagttcag	gcacgggtca	cccgaagtgt	480
	cacctctctg	ttttttcccc	atccatctg	aggaagttaa	agagatccct	cacaggtacc	540
	gtggctctcg	gtgccctcgc	acttccaaca	gcgggttcgg	gccaggaga	ctcgtccga	600
	cctccaccac	aatggcgggc	agtgtggggc	gcgcaaccag	aagtgcggcc	gcgcacctga	660
60	cccagcttcc	gcctgcacct	agagctcagc	gcaccagccc	ggctcagcca	gacgaaggca	720

aacgaagaga tgcggatccc tggaggactg gccccaccgt gaacaaaaca ggaagcattc 780  
 caggaagact gcgggggtgg gctcgtgccg aatc 814

5 <210> 69  
 <211> 788  
 <212> DNA  
 <213> Homo sapiens

10 <220>  
 <221> SITE  
 <222> (370)  
 <223> n equals a,t,g, or c

15 <400> 69  
 gaattcggca cgaggcaatt ttcaatgaac cttgaatggt aggaagaatt gaagaagaaa 60  
 tcagagcatt ttgacctgc agaaggcagc tgctgtgatg gcaggaggct gaaatggaca 120  
 tggcctggca gaagagtatt atgggggtgtg tgtgttgga gccatctggc ctgtacaatt 180  
 tggagaaaaca atactttttt tttctttctc tgcaagctgg gcttcctgtg attgtgtcct 240  
 20 caggctgcac aaaaatagcg tatggccttg ctgtgtattc accttcactc taaaatagct 300  
 agaacatttt cctctctctt ttaaaaagtt tttaaaatga gggtagact cttgtaggaa 360  
 aaggtagaan tcttaataac agtactcatg ttgacaaacc tttctcgtca aaattcctat 420  
 gtaatacaaga ctcttattaa atatgaacaa atgtaatgta tggaaattaa tgtttaccct 480  
 caaggtaaaa gctgaaatgg atttataaag aattatttta aacagcaata atgtttgagg 540  
 25 ggtgggggaa gtgagaaaaa tgaaatttta aatcacatgt ttatgactat gaagctagac 600  
 tttaaaaata ggtcagttag ggtatgactc ttataataca aaagtttatt tggatataca 660  
 aggtattata gctaattgat tttttaatta tattcactaa tacttgtaaa agatcattca 720  
 atttataaag tttccaaaat aaacctgttt aaagtgtcaa aaaaaaaaaa aaaaaaaaaa 780  
 aaactcga 788

30  
 <210> 70  
 <211> 791  
 <212> DNA  
 35 <213> Homo sapiens

<400> 70  
 gaattcggca cgagctcaag gctaaaaatct tgatctctcc tgaatatgag gaggtgtgtt 60  
 aggcattgtt tggggattgg attaatagtg ttaaaaaatt tgtattttca caaaaatagc 120  
 40 atgtacctat caccctaaact cagcagcttt caagaagctt ttcttttttt ctttcttatt 180  
 ttaaaaaaatc ctttaacctt atgtagttag tatatctttt ttaaaaagta gaaaatcatg 240  
 taaccttagg atttttagtt ttaatgtaga gtttcacaaa tttccatctt tagtaagaca 300  
 aaagggtcac atattggctg tctccttcaa ctatactttc ttcagtataa aatatgttta 360  
 ccatggttgt cattatcgag cagcgaactg catgtagtag tctatgctaa gtgttttaca 420  
 45 taatcattta aagctcacta aggccttagg agtaattatt atcctcccat caaaaaggta 480  
 agtgaatgt taacctgaag tttgactact ttaggtctct gagctagtaa gtacaatagc 540  
 caggtttcaa accaagatcc ttttaactgc agcacctgtg ccttatctgg tagcgtcatc 600  
 ttggttcata catttaaaaa agagtatatc atgtgccggg tgccctggct catgcctgta 660  
 atcccagcac tttgggaggc cgaggagggc ggatcaccag gtcaggagtt tgagactgac 720  
 50 caataagggtg aaatcctgtc tctactaaaa aaaaaagggg gggcccgtac ccaatcgccc 780  
 aaaaagatcg t 791

<210> 71  
 55 <211> 804  
 <212> DNA  
 <213> Homo sapiens

<400> 71  
 60 gaattcggca cgagcggcac gagcttgaaa tggcgtcttc tgatgaacac tcattccatcc 60

	ttcaagggtct	actctctcat	cacagcttgt	gactcttcca	ctttttgaac	tggtgtttcc	120
	cattccccagt	tcacagagcc	ctttctcatt	gaactattta	tctgagttcc	ctctgccgga	180
	acatgagcca	tgccatagagt	agccacctag	tagtgagtga	cagctctgtg	ctggatgcac	240
	ataaatggtc	tcctttaact	gccatgagsc	ctaaagaagg	tttgctacag	ctattttaca	300
5	gatggggaaa	actgacagag	agatatatta	gaattgccca	catgcaaata	tgtgctgagt	360
	cttggatttg	catctttatc	gtgactccac	ggagacccac	cctctaagac	cagagccagt	420
	gtctatttca	tcttttgtct	ctgcagcggt	cagcatggca	ctgtcttggc	ttacaaaatc	480
	tgctctatgc	ttgctgactg	ctgaatgaat	gaatgaatga	ataggtagtc	acaaagaatg	540
	tttagaatgt	ttctcagaca	ggctgagaaa	aaacacaacg	aaacattatt	tccgtttgga	600
10	aagttttttt	atttttgtgt	tcagtactga	agtaaaacaa	aaatctgaat	aacagctgca	660
	ccgttaaaaa	tgaaattacc	aatatatgaa	ctctaggcat	catgcatata	taattttttg	720
	tagataactt	ttcttctcat	tttcttcttc	attctcttca	tctttttctt	tttgtttgag	780
	caaaaaaaaa	aaaaaaaaac	tcga				804
15	<210> 72						
	<211> 783						
	<212> DNA						
	<213> Homo sapiens						
20	<400> 72						
	gaattcggca	cgagctaaaa	cttacaatga	catgttgttg	cttgctctgt	aagctccaag	60
	gcattttttt	tttcagtttt	aattcaagt	ttctaaaaag	tattttgggt	acaaccagaa	120
	ctctctctgc	tccttggtatt	ggagtcagt	tgaaagggaac	acagtgggct	ctgggggtcag	180
25	ctagacctgg	atgtggatca	cagctcacct	cttcattggg	aggcctcagg	caagtatttt	240
	gccaacctca	cctacaaaag	catgatgcta	agctcwtttc	agtttagttg	tggatatcag	300
	agcatatgta	tacaatgcct	gccatagtga	gtgcctggcc	cttggcagac	tgtcaaatgg	360
	agctatggag	cagcagcggg	agtaaatatta	ttatctagac	cttatctgtc	cttttaaact	420
	cagttcagat	tccttctcct	ttttaaatta	ctgcaacctg	attttacctg	cccctgcctc	480
30	caagttgctg	tatcagtttag	cctctgaaca	attcatttag	caattttaat	tatatattgc	540
	ttcttgacac	tgctttgtga	tcttaaaaaac	tctgcttcaa	atacgtactt	ggttgctttt	600
	cctgagtgtc	gttaattcct	gctctaacgg	actaaagtaa	tttgaaggca	ggactagggt	660
	ttatgcatgg	cacacagtct	ggtgccttac	atgtaactac	tcacaaaactt	ttttgatcca	720
	aaatttagaa	acttcacacg	cattcataag	aaatcaataa	aaaaaaaaaa	aaaaaactcg	780
35	tag						
	<210> 73						
	<211> 1523						
40	<212> DNA						
	<213> Homo sapiens						
	<220>						
	<221> SITE						
45	<222> (1)						
	<223> n equals a,t,g, or c						
	<220>						
	<221> SITE						
50	<222> (8)						
	<223> n equals a,t,g, or c						
	<220>						
	<221> SITE						
55	<222> (15)						
	<223> n equals a,t,g, or c						
	<400> 73						
	nggggggncc	cccenttttt	tttttttttt	tttttttttt	ttcagttcta	ctattattta	60
60	tttttttaaa	tatttttgaa	aaaatataat	tttttttaca	tattttcaac	ttaaacacta	120

	ttcacactga	acacgtatgg	cagcttaacc	tacccaaata	tgaagtttaa	gaagccaaaa	180
	ctgttctagc	tttgttaaaa	gttgtgctgc	agactctcgt	gatggttaac	aaagcaagga	240
	aaagcaccac	tcaaatacata	atgttacagt	atctttgttc	agctggatta	tgggttggtg	300
	ttggtcatat	gttagactcc	atacaggcat	agctatgatg	cagtgaatcc	cttagaagtt	360
5	acaattctca	aattacatac	ttcctcagat	gtaacattag	aactcaatat	ttctaacaat	420
	aacataccag	aaaaggctgg	actggcactc	atctgctgac	taacttgtag	cctcagtaat	480
	atgacatact	tgcctttaac	aaattatctc	aaattaacta	acagaccttc	agaaaatgga	540
	gattcttttt	gatggggaca	taatcaaatt	taagtctgag	aaatatgctt	aacagttgga	600
	actcaaatta	aatgtactga	ttttaaaagt	tagacattaa	caagtgatag	attagcctca	660
10	aaaaaagaca	atttggtaag	gtttaggtct	tttaatttgg	tgcttgttca	caacttgact	720
	ggtgcttctt	tccttgctgt	cttcacatca	agccatgggg	ccaattctat	tttcagtaaa	780
	tgtttgacag	ctttttactt	agtaacagtc	tcagcacttt	tattaagcat	gcaagactaa	840
	caaaaacttt	ggcaatgcat	aagtgttaaca	cagtgcacaag	agagctttta	caattaagtc	900
	ttctaatact	gccttcacag	tgtggaaatt	gtgtcacatc	caccaaaga	gggccccgtc	960
15	tactcaaata	tttccgtact	tcaccccagg	aacaaactcc	tttgattttg	gattcagatt	1020
	gctcttgacc	acaagatctt	ccagagaaga	gccatcactg	ataacaaggt	cattaaactg	1080
	gtcttggatt	tggtccatag	tttgtgggag	atctcgagct	ggaataaacc	attcatgctc	1140
	ttcttctctt	tccagcattt	cttggaaca	gcgttcaata	aattcttctt	cccataactc	1200
	ctcttctatt	tgtctgttga	attcttcttc	attttccatc	cacatgtact	ctgcaaattg	1260
20	attgtcatct	tcatgagaat	gaccgttaat	aatcacatct	tcattgatga	tgcttgggct	1320
	agtactgctg	cgacttggat	ctttcatggc	tgatgttggg	tgtcgttttt	aacccaatgc	1380
	acagcagcgg	ggacggcagc	caacgaatcc	tgtcggcctc	cgcggatctc	cacaggcagc	1440
	gccgctcccc	cgctcgacgt	gcgcttcgcc	cgccgcctcc	cttctcccgg	acgcgtgggc	1500
25	ggacgcgtgg	gcgacgcgt	ggg				1523
	<210> 74						
	<211> 758						
	<212> DNA						
30	<213> Homo sapiens						
	<400> 74						
	gaattcggca	cgagacasgg	tttcacccctg	ttggccagga	tggtctcaat	ctcttgacct	60
	cgtgatctgc	ctgcctgggc	ctcccaaagt	gctaggatta	caggcatgag	ccactgtgcc	120
35	cggcctttgt	tttttgagac	cttttttatt	ttgttgtcac	ccaggctgaa	gtgcagtggc	180
	acaaacacag	ttcactacag	ccttgacctc	ctgggctcaa	gcaattctgc	ctcagtccca	240
	caagtaggtg	ggcttacaaa	tgcacagcat	gacacctggc	ttatttttgt	attttgtgtg	300
	tgtgtgtgtg	agccactgcg	caggccttgg	gcagctttct	tgatctctgt	tacctcatct	360
	ataaaatgat	gataataata	gcttctccct	tattggggaa	ttgtaatgat	taaatagat	420
40	aacatgtaaa	atgctcagta	caggccaggc	atggtggctc	acgcttgcaa	tcccagcact	480
	ttgggaggct	gaggctgcta	gatctcttga	ggccagcagt	taagaccagc	ctggccaata	540
	tggtgaaacc	ctgtgtctac	caaaaaatac	agaaagtcag	ccaggcatgg	tggtgcatgc	600
	ctgtggtccc	agctactcag	aggctgaggt	gggagaatca	cttgagcccc	ggagacagaa	660
45	gttgaagtga	gccaagatgg	cgccactgca	ctctagcatg	ggctacagag	tgagagcctc	720
	tctcaaaaaa	aaaaaaaaaa	aaaaaaaaaa	aactcgta			758
	<210> 75						
	<211> 1096						
	<212> DNA						
50	<213> Homo sapiens						
	<400> 75						
	ccccacggct	cccatggcct	cttctctgcg	taccgtgtgg	aggccctaac	cctgcgtggc	60
55	atcaatagct	tcgcccagta	caagtatgac	ctggtggcag	tgggcaaggc	tttgaggggc	120
	atgttcgca	agctcaacca	cctcctggag	cgcctgcacc	agtccttctt	cctctacttg	180
	ctccccggcc	tctcccgtt	cgtctccatc	ggcctctaca	tgcccgctgt	cggtctcttg	240
	ctcctggctc	ttggtctcaa	ggctctggaa	ctgtggatgc	agctgcatga	ggctggaatg	300
	ggccttgagg	agcccggggg	tgcccttgcc	cccagtgta	cccttcccc	atcacagggt	360
60	gtggggctgg	cctcgctcgt	ggcacctctg	ctgatctcac	aggccatggg	actggccctc	420



	tatgtcctgc	cagtgtctggg	ccaacacgtt	gccaccacgc	acttcccagt	ggcagaggct	480
	gaggctgtgg	tgctgacact	gctggcgatt	tatgcagctg	gcctggccct	gccycacaat	540
	acccaccggg	tggttaagcac	acaggcccca	gacaggggct	ggatggcact	gaagctggta	600
	gccttgatct	acctagcact	gcagctgggc	tgcatcgccc	tcaccaactt	ctcactgggc	660
5	ttcctgtctg	ccaccaccat	ggtgcccact	gctgcgcttg	ccaagcctca	tgggcccccg	720
	accctctatg	ctgccctgct	ggtgctgacc	agcccggcag	ccacgctcct	tggcagcctg	780
	ttcctgtggc	gggagctgca	ggaggcgcca	ctgtcactgg	ccgagggctg	gcagctcttc	840
	ctggcagcgc	tagcccaggg	tgtgctggag	caccacacta	cggcgccttg	ctcttcccac	900
	tgtgtccct	gggcctctac	ccctgctggc	tgcttttctg	gaatgtgctc	ttctggaagt	960
10	gagatctgcc	tgtccgggct	gggacagaga	ctccccagg	acccattctt	gcctccttct	1020
	ggggaaataa	atgagtgtct	gtttcagcar	mwaaaaaaaa	aaaaaaaaaa	aaaaaaaaaa	1080
	aaaaaaaaag	gcggcc					1096
15	<210> 76						
	<211> 1230						
	<212> DNA						
	<213> Homo sapiens						
20	<400> 76						
	cacgagtgcc	gctaacccttc	ttcatccttt	ggtggcacaag	tagaaagatt	ccagaattaa	60
	ctcgaccttt	ctaaagacct	gggctcagag	gcagctggca	ctgactgagc	accactatg	120
	tgccaggcac	tgtgctgaat	gcattagatc	atcaattatg	aatttgacac	caaggacctg	180
	gtgtgcctgg	gcctgagcag	catcgctggc	gtctggtacc	tgctgaggaa	gcactggatt	240
25	gccaacaacc	tttttggcct	ggccttctcc	cttaatggag	tagagctcct	gcacctcaac	300
	aatgtcagca	ctggctgcat	cctgctgggc	ggactcttca	tctacgatgt	cttctgggta	360
	tttggcacca	atgtgatggt	gacagtggcc	aagtccttcg	aggcaccaat	aaaattgggtg	420
	tttccccagg	atctgctgga	gaaaggcctc	gaagcaaaca	actttgccat	gctgggactt	480
	ggagatgtcg	tcattccagg	gatcttcatt	gccttgctgc	tgcgctttga	catcagcttg	540
30	aagaagaata	cccacaccta	cttctacacc	agctttgcag	cctacatctt	cggcctgggc	600
	cttaccatct	tcattcatgca	catcttcaag	catgctcagc	ctgccctcct	atacctgggtc	660
	cccgcctgca	tcgggttttcc	tgctctgggt	gcgctggcca	agggagaagt	gacagagatg	720
	ttcagttatg	aggagtcaaa	tcctaaggat	ccagcggcag	tgacagaatc	caaagagggga	780
	acagaggcat	cagcatcgaa	ggggctggag	aagaaaagaga	aatgatgcag	ctggtgccccg	840
35	agcctctcag	ggccagacca	gacagatggg	ggctgggccc	acacaggcgt	gcaccggtag	900
	agggcacagg	aggccaaggg	cagctccagg	acagggcagg	gggcagcagg	atacctccag	960
	ccaggcctct	gtggcctctg	tttccctctc	cctttcttgg	ccctcctctg	ctcctccccca	1020
	caccctgcag	gcaaaaagaaa	ccccagctt	ccccctccc	cgggagccag	gtgggaaaag	1080
	tgggtgtgat	tttttagattt	tgtattgtgg	actgattttg	cctcacatta	aaaactcatc	1140
40	ccatggccag	ggcgggcccac	tgtgctcctg	gaaaaaaaaa	aaaaaaaaaa	aaaaaaaaaa	1200
	aaaaaaaaaa	aaaaaaaaaa	ggggaggggc				1230
45	<210> 77						
	<211> 911						
	<212> DNA						
	<213> Homo sapiens						
50	<400> 77						
	tcgacccacg	cgtccgtctt	cctaaaaggg	atgccctcca	aagaaatttt	aaaagaatct	60
	tatcaagggg	ccctggagaa	gaaagggatg	tgagggtcaa	gtcacactt	tgaggggaaa	120
	tagaaagagg	gctcctttct	gagaaagaag	aattttcaag	agtccaagag	aaccaaaaat	180
	tcaggaccca	ggagggttaag	cattcctggt	tttgcaagct	tcacagacca	tttgagttag	240
	tgggtttttc	aggtgacatt	taaatgaaca	aataatatcc	atgtctcagg	gtcagaaatg	300
55	gtactttgca	actgattctg	tcctctctga	gaggctcttg	caagactgag	agggtgggat	360
	gacttaatga	acattaaaaa	caatgttatt	aggckggata	tggtggcaca	tgctgttaat	420
	tctagcattt	tgggargctg	aggtgggcag	gcccargart	tcaagaccag	tctgggcaac	480
	atggtgagac	cctgtatcta	ataaaaaatac	aaaaatttag	ccaggcatgg	tggcacacac	540
	ctggagtccc	agctactcag	gagactgagg	tgggaagatc	acctgagctc	agggaagtcga	600
60	ggctgcagtg	agccaagatt	gcactactgc	actctagcct	acatggatag	gagttagacc	660

	tgtttgaaaa acaaaaaaca atcaaaaaaca aaaaaaaaca acccacacaa tgttatTTTT	720
	aaaatactga ggggagagaa gttggggaaa aaaaggggaaa acctaaaact ctccataatc	780
	ctaccatcag aaaattacac taatgtgata agtgactttc tcccctctga atctccaatt	840
	ccattacttg tagtaaatat gaatcttatt ccacaaactc agacatgcaa aaaaaaaaaa	900
5	aaaggcgccg c	911
	<210> 78	
	<211> 488	
10	<212> DNA	
	<213> Homo sapiens	
	<220>	
	<221> SITE	
15	<222> (324)	
	<223> n equals a,t,g, or c	
	<220>	
	<221> SITE	
20	<222> (438)	
	<223> n equals a,t,g, or c	
	<220>	
	<221> SITE	
25	<222> (484)	
	<223> n equals a,t,g, or c	
	<400> 78	
	accgcagggg ctcccgacc ctgactctgc agccgaaccg gcacggtttc gtggggaccc	60
30	aggcttgcaa agtgacggtc atttctctt tctttctccc tcttgagtcc ttctgagatg	120
	atggctcttg gcgcacggga gctacccggg tctttgtcgc gatggtagcg gcggctctcg	180
	gcgccacccc tctgctggga gtgagcgcca ccttgaactc ggttctcaat tccaacgcta	240
	tcaagaacct gcccccaccg ctggcgccgg ctgccccgca cccaaggctc tgcagtcagc	300
	gccgcgccgg gaatcctgta cccngggcgg gaataagtac cagaccattg acaactacca	360
35	gccgtacccc ttgcgcaaaa gaacraaaga aatttgccgc actgaaataa atttacttgc	420
	gcctaattcc ccaccccncc cggaaagggg aaacccccgg gccgtttttc caaattcttt	480
	tttnttcc	488
	<210> 79	
40	<211> 753	
	<212> DNA	
	<213> Homo sapiens	
	<220>	
	<221> SITE	
45	<222> (745)	
	<223> n equals a,t,g, or c	
	<220>	
	<221> SITE	
50	<222> (752)	
	<223> n equals a,t,g, or c	
	<400> 79	
	gaattcggca cgagcggcgg ggggtccatcc accccggtga gcaggcccaa ggcagcgggg	60
	gcccacaccc ctcacacgca aaactggctt cttctgggtca ctggtgtctg aaaccaaate	120
	cagagcagcc tgtggcctgt aaagcatata tttctaata ctgcagactg gtgggatcat	180
	aggagccttc tgaatgacca ggactgcttt ctttggagct gatgaaaatg tactctttta	240
60	gcgtgttaga aatcaactgt tttattttgt ttctttggcc aagctgggtc tagtgtttct	300

	tttgcctggga atagactttc aaaagttgta cttctatcaa gaaacaaaac tgcccttgca	360
	gaaatttcag gtcttttggt aagcctgtat tggctttaag gtgcagtatt ttttaaat	420
	ttatttatag aaagaatcta taaattcttg gggaagtgtg ttataagctt taataattac	480
	attgagctgc acctcagtggt tgtgtcatta acatgcagtg gggtaatat ctgaggcctc	540
5	agatgacttt gtgccttttg gaataaaggg taaaataaac tctcccagag taagagctgt	600
	atcgtgaatt gtcatactaa ttattgaggg ggacttatgt gctttttattg aatggagtgc	660
	tttacaattt ttatttttaa atgggggttg gatccttgga atatttcaat aaaattgata	720
	aaatataaaa aaaaaaaaaa agggnggccg cnc	753
10	<210> 80	
	<211> 2138	
	<212> DNA	
	<213> Homo sapiens	
15	<400> 80	
	tggaatgata tggactcccc tttcccacgg atgtgatcca gcataggtta cggcaaatcg	60
	aagcagggta caaacaagag gtggagcagc tacgtcgaca ggtgcgtgac tcagatgagr	120
	ctggacatcc gtcactgctg tgcccctcca gcagagcccc catggactat gaggatgatt	180
20	ttacatgttt gaaggagtca gatggcagtg atactgagga ttttggctct gatcacagtg	240
	aagactgcct ttcagaagca agctgggaac ctgttgataa gaaagagact gaggtgactc	300
	gctgggttcc agaccatatg gcatcacact gctataactg tgactgtgaa ttctggttgg	360
	ccaaacgaag acaccattgc agaaattgtg ggaatgtatt ttgtgctgga tgctgccacc	420
	tgaagctgcc cattcctgat cagcaactct atgaccagtg tctcgtctgt aactcatgtt	480
25	acgraacaca ttcaagtctc tcgtgccagg gaactcatga gccaacagct gaagaaaccc	540
	attgctacag cttccagttg aatgccgggg agaaacctgt ccaattttag caggtttgaa	600
	gggaggatct tcttcagttg tagtttgga ggctccttg tgtggctcat gaaatcacag	660
	agctcagaga taccatcttg agaaatcctc cttggtatca tgaaactgga gcagaggaat	720
	tgcaatttag caggaggctc tctactggtg ataccctcac cttggggtaa tggctcctaac	780
30	ccagacccag ggtctggaag cttaatgttg agttggtgac tccagcctct ttctcctgga	840
	ggtcacaaaga tgatgattgc gtatagtttg cctggtgcaa agtgcccaa acagcaatag	900
	aaaggcatat gtataacca actccaagtg ataaccagac ccactctctc tccaccttga	960
	caaaagcaga ttatagtata caaggtagga attcctgtcc tatttgagat gaactatata	1020
	ctgtacctct gtgctctgtg tctgcatgaa ggctcagcct ttagaggcac tccttctagt	1080
35	tgcattagta ctgtcttctc gtggagtttg gtttgaagac tggctcagca agtggagggt	1140
	tcaatgtatt tttcagtttg ctcacagacc agcattggtg aatattcagt ttaggggaac	1200
	agttctaggg agtgagacat tttgggagc agaggaaaac tctgctgatg ttcggtctctg	1260
	gcaaacattg agttattttg agctgtgaag gcagtcgtct ctgttacaca gtggcagctc	1320
	ttgagttatg cactgtgaag aatgagaagg gaaaagcaaa aattatcctt gtgaaatata	1380
40	tgctgattgt gccctactct ttgcacctga cttttcctag ttgtcctggt gctaacacag	1440
	gagctacacm ttgatcctct cctggcatga aaataaaaca aaggttttcg ttgttctgt	1500
	tccattgccc atttccccca tgttgtcttt cccttggtcg atgcctctc tgggtcacat	1560
	tgcttcttat cctgaacact tgacacctg agggtagaat ttagcgtttg gtttttacct	1620
	cctagcatat gctgtttggt atgtgagggg ttcagtacaa atgctgctgt ctatttctgt	1680
45	gcacttaaca atggaacca aacagaagag aataaagcct tgataccaaa attgggaaag	1740
	aacatgtgtc catttggacc aaacgttgtt ggtttttaaa aaattttatt ttgtttttt	1800
	gtttttgttt ttgtttttt tcactttaat atgtaccagt ggcacttaac caaaagatac	1860
	agtgatatag ccatgtatct gtctacttag cgtggctgtt ttgagggaact gtcccatcag	1920
	tgaacaaact gcatggcctt ggagagagac tctgggctct tggctcagat gtgttcatca	1980
50	aatactcctt tcagagctgt tgtgggtgta agtgacatga tgtggccaaa aatccaaact	2040
	gtgcagttgc gttgtgacaa acatgcaatg tgctgtaaaa attcaatata gtttaataa	2100
	aatctctata ttagtaaaaa aaaaaaaaaa aaactcga	2138
55	<210> 81	
	<211> 1327	
	<212> DNA	
	<213> Homo sapiens	
60	<220>	

<221> SITE  
 <222> (5)  
 <223> n equals a,t,g, or c

5 <220>  
 <221> SITE  
 <222> (7)  
 <223> n equals a,t,g, or c

10 <220>  
 <221> SITE  
 <222> (9)  
 <223> n equals a,t,g, or c

15 <220>  
 <221> SITE  
 <222> (10)  
 <223> n equals a,t,g, or c

20 <220>  
 <221> SITE  
 <222> (1205)  
 <223> n equals a,t,g, or c

25 <400> 81  
 aaccnangnn taccggtccg gaattcccgg gtcggaccca cgcgtccgcg gcgggcgacg 60  
 cacgtcgagc gggggagcgg cgctgcctgt ggagatccgc ggaggccgac aggattcggt 120  
 ggctgccgtc cccgctgctg tgcattgggt taaaaacgac aaccaacatc agccatgaaa 180  
 gatccaagtc gcagcagtac tagcccaagc atcatcaatg aagatgtgat tattaacggt 240  
 30 cattctcatg aagatgacaa tccatttgca gagtacatgt ggatggaaaa tgaagaagaa 300  
 ttcaacagac aaatagaaga ggagttatgg gaagaagaat ttattgaacg ctgtttccaa 360  
 gaaatgctgg aagaggaaga agagcatgaa tggtttatcc cagctcgaga tctcccacaa 420  
 actatggacc aaatccaaga ccagtttaac gaccttgcta tcagtgatgg ctcttctctg 480  
 gaagatcttg tggtaagag caatctgaat ccaaatgcaa aggagtgtgt tcctggggtg 540  
 35 aagtacggaa atatttgagt agacggggcc ctcttttggg ggatgtagca caatttccac 600  
 actgtgaagg cagtattaga agacttaatt gtaaaagctc tcttgctact gtgttacact 660  
 tatgcattgc caaagttttt gttagtcttg catgcttaac aaaagtgctg agactgttac 720  
 taagtaaaaa gctgtcaaac atttactgaa aatagaattg gccccatggc ttgatgtgaa 780  
 gacagcaagg aaagaagcac cagtcaagtt gtgaacaagc accaaattaa aagacctaaa 840  
 40 ccttaccaaa ttgtcttttt ttgaggctaa tctatcactt gttaatgtct aaactttaaa 900  
 atcagtatcat ttaatttgag ttccaactgt taagcatatt tctcagactt aaatttgatt 960  
 atgtcccat caaaaagaat ctccattttc tgaaggctctg ttagttaatt tgagataatt 1020  
 tgtaaaggc aagtatgtca tattactgag gctacaagtt agtcagcaga tgagtgccag 1080  
 tccagccttt tctggatgtg tattgttagr aatattgagt tctaattgta catctgaggr 1140  
 45 agtatgtaat tgagrattgt aacttctaag ggggttcaact catcatrgct atgcctgtat 1200  
 ggrgntctwa ccatatgacc mataccamcc cwttaatccca gctgraccaa rgrtacckgt 1260  
 aaccattwwg gatttgaggg gkggcccttc ccyggcyttg kttwaccmt ccacggagaa 1320  
 tctggca 1327

50 <210> 82  
 <211> 758  
 <212> DNA  
 <213> Homo sapiens

55 <400> 82  
 gaattcggca cgagacacgg tttcaccttg ttggccagga tgggtctcaat ctcttgacct 60  
 cgtgatctgc ctgcctcggc ctcccaaagt gctaggatta caggcatgag ccactgtgcc 120  
 cgccctttgt tttttgagac cttttttatt ttgtgtcac ccaggctgaa gtgcagtggc 180  
 60 acaaacacag ttcactacag ccttgacctc ctgggctcaa gcaattctgc ctcagtccca 240

caagtaggtg ggcttacaaa tgcacagcat gacacctggc ttatttttgt attttgtgtg 300  
 tgtgtgtgtg agccactgcg caggccttgg gcagctttct tgatctctgt tacctcatct 360  
 ataaaaatgat gataataata gcttctccct tattggggaa ttgtaatgat taaatgagat 420  
 aacatgtaaa atgctcagta caggccaggc atggtggctc acgcttgcaa tcccagcact 480  
 5 ttgggaggct gaggctgcta gatctcttga ggccagcagt taagaccagc ctggccaata 540  
 tggtgaaacc ctgtgtctac caaaaaatac agaaagtcag ccaggcatgg tgggtgcatgc 600  
 ctgtgggtccc agctactcag aggctgaggt gggagaatca cttgagcccc ggagacagaa 660  
 gttgaagtga gccaaagatgg cgccactgca ctctagcatg ggctacagag tgagagcctc 720  
 tctcaaaaaa aaaaaaaaaa aaaaaaaaaa aactcgta 758

10

<210> 83  
 <211> 48  
 <212> PRT  
 15 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (48)  
 20 <223> Xaa equals stop translation

<400> 83  
 Met Gly Ser Cys Ala Ala Phe Leu Leu Ala Ala Leu Ser Leu Leu Gly  
 1 5 10 15  
 25 Val Leu Gly Gly Tyr Pro Gly Arg Arg Ala Phe Ile Leu Pro Asn Arg  
 20 25 30  
 30 Arg Ser Leu Arg Gln Trp Leu Glu Val Ser Leu Gly Pro Val Ser Xaa  
 35 40 45

35

<210> 84  
 <211> 38  
 <212> PRT  
 <213> Homo sapiens

40

<220>  
 <221> SITE  
 <222> (38)  
 <223> Xaa equals stop translation

45

<400> 84  
 Met Asn Glu Ala Pro Pro Leu Ser Ser Ser Ser Ile Cys Phe Ile Leu  
 1 5 10 15  
 50 Phe Tyr Phe Phe Pro Leu Leu Pro Pro Leu Ser Ser Thr Cys Phe Ser  
 20 25 30  
 Lys Gly Asn Arg His Xaa  
 35

55

<210> 85  
 <211> 53  
 <212> PRT  
 60 <213> Homo sapiens

```

5  <220>
    <221> SITE
    <222> (53)
    <223> Xaa equals stop translation

    <400> 85
Met  Cys  Gln  Asn  Arg  Glu  Ser  Val  Leu  Val  Leu  Leu  Ile  Glu  Ser  Asn
   1              5              10              15

10  Met  Phe  Ser  Phe  Tyr  Leu  Leu  Phe  Ser  Phe  Tyr  Ile  Val  Phe  Ser  Phe
              20              25              30

    Phe  Ile  Val  Leu  Arg  Pro  Leu  Pro  Arg  Asn  Glu  Ser  Ile  Lys  Lys  Ile
              35              40              45

15  Gly  Val  Ile  Phe  Xaa
              50

20  <210> 86
    <211> 26
    <212> PRT
    <213> Homo sapiens

25  <220>
    <221> SITE
    <222> (26)
    <223> Xaa equals stop translation

    <400> 86
Met  Thr  Val  Leu  Ala  Lys  Arg  Leu  Val  Leu  Phe  Leu  Gly  His  Ile  Phe
   1              5              10              15

35  Leu  Leu  Leu  Cys  Val  Arg  Ile  Leu  Asp  Xaa
              20              25

    <210> 87
    <211> 78
    <212> PRT
    <213> Homo sapiens

40  <220>
    <221> SITE
    <222> (43)
    <223> Xaa equals any one of the naturally occurring L-amino acids

45  <220>
    <221> SITE
    <222> (78)
    <223> Xaa equals stop translation

50  <400> 87
Met  Ala  Ala  Arg  Ser  Ala  Leu  Ala  Leu  Leu  Leu  Leu  Leu  Pro  Val  Leu
   1              5              10              15

    Leu  Leu  Pro  Val  Gln  Ser  Arg  Ser  Glu  Pro  Glu  Thr  Thr  Ala  Pro  Thr
              20              25              30

55  <210> 87
    <211> 78
    <212> PRT
    <213> Homo sapiens

60  <220>
    <221> SITE
    <222> (78)
    <223> Xaa equals stop translation

    <400> 87
Met  Thr  Val  Leu  Ala  Lys  Arg  Leu  Val  Leu  Phe  Leu  Gly  His  Ile  Phe
   1              5              10              15

    Leu  Leu  Leu  Cys  Val  Arg  Ile  Leu  Asp  Xaa
              20              25

```

Pro Thr Pro Ile Pro Gly Gly Asn Ser Ser Xaa Ser Arg Pro Leu Pro  
 35 40 45

5 Ser Ile Glu Leu His Ala Cys Gly Pro Tyr Pro Lys Pro Gly Leu Leu  
 50 55 60

Ile Leu Leu Ala Pro Leu Ala Leu Trp Pro Ile Leu Leu Xaa  
 65 70 75

10 <210> 88  
 <211> 38  
 <212> PRT  
 <213> Homo sapiens

15 <220>  
 <221> SITE  
 <222> (38)  
 <223> Xaa equals stop translation

20 <400> 88  
 Met Cys Tyr Ile Pro Gly Ser Thr Gly Gly Gln Cys Trp Pro Trp Cys  
 1 5 10 15

25 Trp Cys Trp Leu Cys Arg Glu Ala Leu Glu Trp Leu Cys Gly Ala Val  
 20 25 30

Ser Ala Gly Pro Ala Xaa  
 35

30 <210> 89  
 <211> 44  
 <212> PRT  
 <213> Homo sapiens

35 <220>  
 <221> SITE  
 <222> (40)  
 <223> Xaa equals any one of the naturally occurring L-amino acids

40 <220>  
 <221> SITE  
 <222> (44)  
 <223> Xaa equals stop translation

45 <400> 89  
 Met Leu Leu Arg Ile Ile His Leu Val Ile Phe Phe Ile Asn Phe Ser  
 1 5 10 15

50 Thr Ser Val Val Ile Val His Tyr Asn Val Leu Asn Tyr Arg Cys Leu  
 20 25 30

55 Leu Lys Cys Arg Cys Arg Val Xaa Lys Tyr Ser Xaa  
 35 40

60 <210> 90  
 <211> 60  
 <212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (60)

<223> Xaa equals stop translation

<400> 90

Met Gln Asn Cys Leu Gly Ser Leu Ile Pro Gly Val Leu Phe Ser Leu  
1 5 10 15

Leu Leu Leu Pro Ser Met Phe Asn Ile Ile Leu Thr Gln Ser Lys Tyr  
20 25 30

Gly Glu Asn Ser Tyr Pro Ala Cys Phe Tyr Ser Ser Ser Asn Phe Pro  
35 40 45

Val Ser Ala Ile Thr Phe Leu Val Gly Val Val Xaa  
50 55 60

<210> 91

<211> 55

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (55)

<223> Xaa equals stop translation

<400> 91

Met Val Val Ile Val Leu Thr Ser Asn Val Cys Ile Cys Gly Tyr Val  
1 5 10 15

Val His Ser Ala Leu Ile Pro Arg Arg Gln Gly Leu Phe Leu Phe Leu  
20 25 30

Phe Leu Val Met Phe Tyr Phe Ser Ile Ala Phe Asn Arg Ile Thr Lys  
35 40 45

Gly Thr Leu Ser Ser Gln Xaa  
50 55

<210> 92

<211> 51

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (51)

<223> Xaa equals stop translation

<400> 92

Met Val Ala Gln Leu Val Gly Cys Val Val Ser Cys Leu Phe Val Leu  
1 5 10 15

Leu Arg Phe Leu Ile Ser Thr Phe Gly Ile Met Ser Phe Asn Gly Phe



20 25 30  
 Val Ile Phe Val Thr Val Leu Ala Ala Tyr Asn Phe Ser Ala Gly Ala  
 35 40 45  
 5 Phe Thr Xaa  
 50  
 10 <210> 93  
 <211> 156  
 <212> PRT  
 <213> Homo sapiens  
 15 <220>  
 <221> SITE  
 <222> (156)  
 <223> Xaa equals stop translation  
 20 <400> 93  
 Met Trp Pro Gln Glu Ala Trp Val Cys Ile Leu Val Leu Leu Gly Thr  
 1 5 10 15  
 25 Arg Val Gly Leu Cys Val Gly Asp Ser Leu Ala Pro Gln Ala Ser Leu  
 20 25 30  
 Ser Tyr Cys Tyr Ile Leu Lys Val Pro Leu Arg Pro Lys Pro Leu Trp  
 35 40 45  
 30 Gln Leu Ser Asn Glu Ser Ile Cys Ser Glu Tyr Arg Val Glu Gly Gly  
 50 55 60  
 Gln Gly His Gln Glu Leu Arg Met Phe Leu Arg Leu Met Arg Pro Arg  
 65 70 75 80  
 35 Tyr Trp Val His Gly Gly Pro Arg Ser Leu Cys Asp Ser Cys Ser Leu  
 85 90 95  
 Leu Pro Pro Cys Leu Asp Pro Ala Ser Ala Gln Lys Ala Asn Ser Leu  
 100 105 110  
 40 Asp Ser Lys Gly Leu Pro Arg Pro Ile Ser Met Ser Cys Ser Cys Gln  
 115 120 125  
 45 Leu Pro Val Pro Ser Leu Asp Leu Ser Ser Cys Leu Ala Pro Ser Leu  
 130 135 140  
 Pro Thr Pro His Ile Phe Thr Asn Lys Arg Lys Xaa  
 145 150 155  
 50 <210> 94  
 <211> 61  
 <212> PRT  
 <213> Homo sapiens  
 <220>  
 <221> SITE  
 <222> (61)  
 60 <223> Xaa equals stop translation

&lt;400&gt; 94

Met Ser His His Ala Arg Pro Tyr Lys Ala Phe Arg Ile Val Ser Cys  
 1 5 10 15

5

Tyr Phe Tyr Leu Phe Ile Ile Val Val Val Ile Ile Leu Leu Leu Tyr  
 20 25 30

10

Pro Ile Ser Gln Gly Trp His Val Ala Asn Ile Val Phe Leu Lys Asn  
 35 40 45

Ile Ser Asp His Ile Leu Val Leu Leu Lys Thr Phe Xaa  
 50 55 60

15

&lt;210&gt; 95

&lt;211&gt; 71

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

20

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (71)

&lt;223&gt; Xaa equals stop translation

25

&lt;400&gt; 95

Met Trp Phe Glu Ile Leu Pro Gly Leu Ser Val Met Gly Val Cys Leu  
 1 5 10 15

30

Leu Ile Pro Gly Leu Ala Thr Ala Tyr Ile His Arg Phe Thr Asn Gly  
 20 25 30

Gly Lys Glu Lys Arg Val Ala His Phe Gly Tyr His Trp Ser Leu Met  
 35 40 45

35

Glu Arg Asp Arg Arg Ile Ser Gly Val Asp Arg Tyr Tyr Val Ser Lys  
 50 55 60

40

Gly Leu Glu Asn Ile Asp Xaa  
 65 70

&lt;210&gt; 96

&lt;211&gt; 37

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

45

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (37)

&lt;223&gt; Xaa equals stop translation

50

&lt;400&gt; 96

Met Val Phe Leu Leu Leu Leu Phe Gly Phe Phe Phe Asp Gly Ser  
 1 5 10 15

55

Leu Arg Ser Pro Leu Leu Leu Ile Ile His Leu Gly Pro Ala Pro Thr  
 20 25 30

60

Phe Leu Gln Ile Xaa

45

35

5 <210> 97  
 <211> 60  
 <212> PRT  
 <213> Homo sapiens  
  
 10 <220>  
 <221> SITE  
 <222> (60)  
 <223> Xaa equals stop translation  
  
 15 <400> 97  
 Met Leu Cys Gln Thr Ile Pro Leu Cys Asn Arg Leu His Ile Val Phe  
       1                  5                  10                  15  
 Met Ile Leu Ile Lys Leu Tyr Val Glu Thr Glu Cys Glu Val Lys Ser  
                   20                  25                  30  
 20 Glu His Lys Lys Ile Met His Asp Glu Ile Ala Tyr His Phe Ile Gly  
           35                  40                  45  
 Tyr Leu Leu Cys Ile Tyr Thr Leu Arg Pro Leu Xaa  
 25       50                  55                  60  
  
 30 <210> 98  
 <211> 44  
 <212> PRT  
 <213> Homo sapiens  
  
 35 <220>  
 <221> SITE  
 <222> (44)  
 <223> Xaa equals stop translation  
  
 40 <400> 98  
 Met Ser Val Ser Ser Asn Leu Trp Gln Thr Leu Ile Leu Leu Leu Ser  
       1                  5                  10                  15  
 Leu Trp Phe Cys Leu Phe Pro Glu Cys His Ile Val Gly Ile Ile Gln  
           20                  25                  30  
 45 Leu Cys Arg Leu Phe Arg Leu Pro Ser Phe Thr Xaa  
       35                  40  
  
 50 <210> 99  
 <211> 32  
 <212> PRT  
 <213> Homo sapiens  
  
 55 <220>  
 <221> SITE  
 <222> (32)  
 <223> Xaa equals stop translation  
  
 60 <400> 99  
 Met Cys Cys Arg Ala Gly Gly Ser Gln Ser Pro Gln Val Met Val Val

46

1                      5                      10                      15  
 Leu Ile Ile Ile Leu Gly Pro Trp Gly Gly Val Arg Ile Asp Ala Xaa  
                          20                      25                      30  
 5  
  
 10 <210> 100  
     <211> 180  
     <212> PRT  
     <213> Homo sapiens  
  
 15 <400> 100  
 Met Tyr Ser Cys Leu Leu Leu Pro Asp Leu Leu Tyr Leu Thr Leu Ser  
     1                      5                      10                      15  
  
 20 Pro Leu Val Val Ala Met Leu Leu Thr Pro His Phe Asn Val Ala Asn  
                          20                      25                      30  
  
 Pro Gln Asn Leu Leu Ala Gly Leu Trp Leu Glu Asn Glu His Ser Phe  
                          35                      40                      45  
  
 25 Thr Leu Met Ala Pro Glu Arg Ala Arg Thr His His Cys Gln Pro Glu  
                          50                      55                      60  
  
 Glu Arg Lys Val Leu Phe Cys Leu Phe Pro Ile Val Pro Asn Ser Gln  
     65                      70                      75                      80  
 30 Ala Gln Val Gln Pro Pro Gln Met Pro Pro Phe Cys Cys Ala Ala Ala  
                          85                      90                      95  
  
 Lys Glu Lys Thr Gln Glu Glu Gln Leu Gln Glu Pro Leu Gly Ser Gln  
     100                      105                      110  
  
 Cys Pro Asp Thr Cys Pro Asn Ser Leu Cys Pro Ser His Thr Gln Leu  
                          115                      120                      125  
  
 40 Thr Lys Ala Asn Thr Leu Ser Leu Phe Phe Phe Phe Ser Phe Phe Leu  
                          130                      135                      140  
  
 Ser Arg Val Ser Leu Leu Ser Pro Arg Leu Glu Cys Asn Gly Arg Ile  
     145                      150                      155                      160  
 45 Leu Ala His Cys Asn Leu His Leu Pro Gly Ser Ser Asn Ser Pro Val  
                          165                      170                      175  
  
 Ser Ala Ser Arg  
                          180  
 50  
  
 <210> 101  
 <211> 212  
 55 <212> PRT  
     <213> Homo sapiens  
  
 <220>  
 <221> SITE  
 60 <222> (45)

<223> Xaa equals any one of the naturally occurring L-amino acids  
 <220>  
 <221> SITE  
 5 <222> (195)  
 <223> Xaa equals any one of the naturally occurring L-amino acids  
 <220>  
 <221> SITE  
 10 <222> (212)  
 <223> Xaa equals stop translation  
 <400> 101  
 15 Met Arg Leu Phe Leu Trp Asn Ala Val Leu Thr Leu Phe Val Thr Ser  
 1 5 10 15  
 Leu Ile Gly Ala Leu Ile Pro Glu Pro Glu Val Lys Ile Glu Val Leu  
 20 20 25 30  
 20 Gln Lys Pro Phe Ile Cys His Arg Lys Thr Lys Gly Xaa Asp Leu Met  
 35 40 45  
 Leu Val His Tyr Glu Gly Tyr Leu Glu Lys Asp Gly Ser Leu Phe His  
 25 50 55 60  
 Ser Thr His Lys His Asn Asn Gly Gln Pro Ile Trp Phe Thr Leu Gly  
 65 70 75 80  
 30 Ile Leu Glu Ala Leu Lys Gly Trp Asp Gln Gly Leu Lys Gly Met Cys  
 85 90 95  
 Val Gly Glu Lys Arg Lys Leu Ile Ile Pro Pro Ala Leu Gly Tyr Gly  
 100 105 110  
 35 Lys Glu Gly Lys Gly Lys Ile Pro Pro Glu Ser Thr Leu Ile Phe Asn  
 115 120 125  
 Ile Asp Leu Leu Glu Ile Arg Asn Gly Pro Arg Ser His Glu Ser Phe  
 130 135 140  
 40 Gln Glu Met Asp Leu Asn Asp Asp Trp Lys Leu Ser Lys Asp Glu Val  
 145 150 155 160  
 Lys Ala Tyr Leu Lys Lys Glu Phe Glu Lys His Gly Ala Val Val Asn  
 45 165 170 175  
 Glu Ser His His Asp Ala Leu Val Glu Asp Ile Phe Asp Lys Glu Asp  
 180 185 190  
 50 Glu Asp Xaa Tyr Gly Phe Ile Ser Ala Arg Glu Phe Thr Tyr Lys His  
 195 200 205  
 Asp Glu Leu Xaa  
 210  
 55 <210> 102  
 <211> 621  
 <212> PRT  
 60 <213> Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (137)

5 &lt;223&gt; Xaa equals any one of the naturally occurring L-amino acids

&lt;400&gt; 102

Met Gly Leu Leu Ser Asp Pro Val Arg Arg Arg Ala Leu Ala Arg Leu  
 1 5 10 15

10

Val Leu Arg Leu Asn Ala Pro Leu Cys Val Leu Ser Tyr Val Ala Gly  
 20 25 30

15

Ile Ala Trp Phe Leu Ala Leu Val Phe Pro Pro Leu Thr Gln Arg Thr  
 35 40 45

Tyr Met Ser Glu Asn Ala Met Gly Ser Thr Met Val Glu Glu Gln Phe  
 50 55 60

20

Ala Gly Gly Asp Arg Ala Arg Ala Phe Ala Arg Asp Phe Ala Ala His  
 65 70 75 80

Arg Lys Lys Ser Gly Ala Leu Pro Val Ala Trp Leu Glu Arg Thr Met  
 85 90 95

25

Arg Ser Val Gly Leu Glu Val Tyr Thr Gln Ser Phe Ser Arg Lys Leu  
 100 105 110

30

Pro Phe Pro Asp Glu Thr His Glu Arg Tyr Met Val Ser Gly Thr Asn  
 115 120 125

Val Tyr Gly Ile Leu Arg Ala Pro Xaa Ala Ala Ser Thr Glu Ser Leu  
 130 135 140

35

Val Leu Thr Val Pro Cys Gly Ser Asp Ser Thr Asn Ser Gln Ala Val  
 145 150 155 160

Gly Leu Leu Leu Ala Leu Ala Ala His Phe Arg Gly Gln Ile Tyr Trp  
 165 170 175

40

Ala Lys Asp Ile Val Phe Leu Val Thr Glu His Asp Leu Leu Gly Thr  
 180 185 190

45

Glu Ala Trp Leu Glu Ala Tyr His Asp Val Asn Val Thr Gly Met Gln  
 195 200 205

Ser Ser Pro Leu Gln Gly Arg Ala Gly Ala Ile Gln Ala Ala Val Ala  
 210 215 220

50

Leu Glu Leu Ser Ser Asp Val Val Thr Ser Leu Asp Val Ala Val Glu  
 225 230 235 240

Gly Leu Asn Gly Gln Leu Pro Asn Leu Asp Leu Leu Asn Leu Phe Gln  
 245 250 255

55

Thr Phe Cys Gln Lys Gly Gly Leu Leu Cys Thr Leu Gln Gly Lys Leu  
 260 265 270

60

Gln Pro Glu Asp Trp Thr Ser Leu Asp Gly Pro Leu Gln Gly Leu Gln  
 275 280 285

Thr Leu Leu Leu Met Val Leu Arg Gln Ala Ser Gly Arg Pro His Gly  
 290 295 300

5 Ser His Gly Leu Phe Leu Arg Tyr Arg Val Glu Ala Leu Thr Leu Arg  
 305 310 315 320

Gly Ile Asn Ser Phe Arg Gln Tyr Lys Tyr Asp Leu Val Ala Val Gly  
 325 330 335

10 Lys Ala Leu Glu Gly Met Phe Arg Lys Leu Asn His Leu Leu Glu Arg  
 340 345 350

15 Leu His Gln Ser Phe Phe Leu Tyr Leu Leu Pro Gly Leu Ser Arg Phe  
 355 360 365

Val Ser Ile Gly Leu Tyr Met Pro Ala Val Gly Phe Leu Leu Leu Val  
 370 375 380

20 Leu Gly Leu Lys Ala Leu Glu Leu Trp Met Gln Leu His Glu Ala Gly  
 385 390 395 400

Met Gly Leu Glu Glu Pro Gly Gly Ala Pro Gly Pro Ser Val Pro Leu  
 405 410 415

25 Pro Pro Ser Gln Gly Val Gly Leu Ala Ser Leu Val Ala Pro Leu Leu  
 420 425 430

30 Ile Ser Gln Ala Met Gly Leu Ala Leu Tyr Val Leu Pro Val Leu Gly  
 435 440 445

Gln His Val Ala Thr Gln His Phe Pro Val Ala Glu Ala Glu Ala Val  
 450 455 460

35 Val Leu Thr Leu Leu Ala Ile Tyr Ala Ala Gly Leu Ala Leu Pro His  
 465 470 475 480

Asn Thr His Arg Val Val Ser Thr Gln Ala Pro Asp Arg Gly Trp Met  
 485 490 495

40 Ala Leu Lys Leu Val Ala Leu Ile Tyr Leu Ala Leu Gln Leu Gly Cys  
 500 505 510

45 Ile Ala Leu Thr Asn Phe Ser Leu Gly Phe Leu Leu Ala Thr Thr Met  
 515 520 525

Val Pro Thr Ala Ala Leu Ala Lys Pro His Gly Pro Arg Thr Leu Tyr  
 530 535 540

50 Ala Ala Leu Leu Val Leu Thr Ser Pro Ala Ala Thr Leu Leu Gly Ser  
 545 550 555 560

Leu Phe Leu Trp Arg Glu Leu Gln Glu Ala Pro Leu Ser Leu Ala Glu  
 565 570 575

55 Gly Trp Gln Leu Phe Leu Ala Ala Leu Ala Gln Gly Val Leu Glu His  
 580 585 590

60 His Thr Tyr Gly Ala Leu Leu Phe Pro Leu Leu Ser Leu Gly Leu Tyr  
 595 600 605

Pro Cys Trp Leu Leu Phe Trp Asn Val Leu Phe Trp Lys  
 610 615 620

5

<210> 103  
 <211> 287  
 <212> PRT  
 <213> Homo sapiens

10

<220>  
 <221> SITE  
 <222> (263)  
 <223> Xaa equals any one of the naturally occurring L-amino acids

15

<400> 103  
 Met Ala Leu Leu Pro Ile Phe Phe Gly Ala Leu Arg Ser Val Arg Cys  
 1 5 10 15

20

Ala Arg Gly Lys Asn Ala Ser Asp Met Pro Glu Thr Ile Thr Ser Arg  
 20 25 30

Asp Ala Ala Arg Phe Pro Ile Ile Ala Ser Cys Thr Leu Leu Gly Leu  
 35 40 45

25

Tyr Leu Phe Phe Lys Ile Phe Ser Gln Glu Tyr Ile Asn Leu Leu Leu  
 50 55 60

30

Ser Met Tyr Phe Phe Val Leu Gly Ile Leu Ala Leu Ser His Thr Ile  
 65 70 75 80

Ser Pro Phe Met Asn Lys Phe Phe Pro Ala Ser Phe Pro Asn Arg Gln  
 85 90 95

35

Tyr Gln Leu Leu Phe Thr Gln Gly Ser Gly Glu Asn Lys Glu Glu Ile  
 100 105 110

Ile Asn Tyr Glu Phe Asp Thr Lys Asp Leu Val Cys Leu Gly Leu Ser  
 115 120 125

40

Ser Ile Val Gly Val Trp Tyr Leu Leu Arg Lys His Trp Ile Ala Asn  
 130 135 140

Asn Leu Phe Gly Leu Ala Phe Ser Leu Asn Gly Val Glu Leu Leu His  
 145 150 155 160

45

Leu Asn Asn Val Ser Thr Gly Cys Ile Leu Leu Gly Gly Leu Phe Ile  
 165 170 175

50

Tyr Asp Val Phe Trp Val Phe Gly Thr Asn Val Met Val Thr Val Ala  
 180 185 190

Lys Ser Phe Glu Ala Pro Ile Lys Leu Val Phe Pro Gln Asp Leu Leu  
 195 200 205

55

Glu Lys Gly Leu Glu Ala Asn Asn Phe Ala Met Leu Gly Leu Gly Asp  
 210 215 220

60

Val Val Ile Pro Gly Ile Phe Ile Ala Leu Leu Leu Arg Phe Asp Ile  
 225 230 235 240



Ser Leu Lys Lys Asn Thr His Thr Tyr Phe Tyr Thr Ser Phe Ala Ala  
 245 250 255  
 5 Tyr Ile Phe Gly Leu Gly Xaa Tyr His Leu His His Ala His Leu Gln  
 260 265 270  
 Ala Cys Ser Val Met Arg Ser Gln Ile Leu Arg Ile Gln Arg Gln  
 275 280 285  
 10  
 <210> 104  
 <211> 32  
 <212> PRT  
 15 <213> Homo sapiens  
 <220>  
 <221> SITE  
 <222> (32)  
 20 <223> Xaa equals stop translation  
 <400> 104  
 Met Ser Arg Leu Leu Leu Leu Phe Gly Arg Leu Cys Ser Leu Trp Cys  
 1 5 10 15  
 25 Leu Ser Trp Leu Tyr Ser Thr Asp Thr Arg Pro Leu Leu Arg Gly Xaa  
 20 25 30  
 30  
 <210> 105  
 <211> 77  
 35 <212> PRT  
 <213> Homo sapiens  
 <400> 105  
 Met Leu Pro Arg Leu Val Leu Asn Ser Trp Ala Cys Pro Pro Gln Pro  
 1 5 10 15  
 Pro Lys Val Leu Glu Leu Gln Ala Cys Ala Thr Ile Ser Ser Leu Ile  
 20 25 30  
 45 Thr Leu Phe Leu Met Phe Ile Lys Ser Ser His Pro Leu Ser Leu Ala  
 35 40 45  
 Glu Ala Ser Gln Glu Gly Gln Asn Gln Leu Gln Ser Thr Ile Ser Asp  
 50 55 60  
 Pro Glu Thr Trp Ile Leu Phe Val His Leu Asn Val Thr  
 65 70 75  
 55 <210> 106  
 <211> 45  
 <212> PRT  
 <213> Homo sapiens  
 60 <220>

<221> SITE  
 <222> (45)  
 <223> Xaa equals stop translation

5 <400> 106  
 Met Val Phe Leu Val Phe Tyr Val Leu Arg Ala Leu Lys Cys Asn Ser  
 1 5 10 15

10 Ser Tyr His Ser Cys Thr Asn Val Leu Thr Gln Ile Ala Ser Gln Ile  
 20 25 30

Asp Lys Thr Leu Asn Asn Phe Ser Leu Lys Lys Cys Xaa  
 35 40 45

15 <210> 107  
 <211> 42  
 <212> PRT  
 <213> Homo sapiens

20 <220>  
 <221> SITE  
 <222> (42)  
 <223> Xaa equals stop translation

25 <400> 107  
 Met Asn Pro Cys Leu Ser Ile Ile Phe Leu Leu Thr Pro Val Leu Leu  
 1 5 10 15

30 Ser His Pro Leu Gln Ser Leu His Phe Leu Leu Lys Val Asp Leu Asp  
 20 25 30

Phe Ser Leu Ser Cys Ser Ile Cys Thr Xaa  
 35 40

35 <210> 108  
 <211> 70  
 <212> PRT  
 <213> Homo sapiens

40 <220>  
 <221> SITE  
 <222> (70)  
 <223> Xaa equals stop translation

45 <400> 108  
 Met Thr Val Tyr Leu Leu Lys Thr His Pro Cys Phe Phe Val Ala Tyr  
 1 5 10 15

50 Gln Met Gln Val Ala Leu Ile Ile Leu Leu Pro Gly Leu Arg Asn Ser  
 20 25 30

55 Lys Thr Val Thr Met Pro Leu Ser Pro Ala Leu Leu Pro Thr Leu Leu  
 35 40 45

Phe Phe Pro Ser Pro Thr Pro Phe Phe His Pro Phe Leu Ser Val Leu  
 50 55 60

60 Cys Cys Phe Lys Tyr Xaa

65                      70

5    <210> 109  
      <211> 49  
      <212> PRT  
      <213> Homo sapiens

10   <220>  
      <221> SITE  
      <222> (43)  
      <223> Xaa equals any one of the naturally occurring L-amino acids

15   <220>  
      <221> SITE  
      <222> (49)  
      <223> Xaa equals stop translation

20   <400> 109  
      Met His Ala Thr Cys Thr Arg Thr Trp Arg Ala Gln Val Ser Leu His  
          1                      5                      10                      15

     Gln Pro Pro Cys Ser Arg Asp Trp Lys Ile Cys His Leu Leu Val Val  
                          20                      25                      30

25   Leu Ser Leu Pro Pro Pro Thr Pro Ala Arg Xaa Pro Glu Phe Leu Asn  
                  35                      40                      45

     Xaa

30

35   <210> 110  
      <211> 193  
      <212> PRT  
      <213> Homo sapiens

40   <220>  
      <221> SITE  
      <222> (193)  
      <223> Xaa equals stop translation

45   <400> 110  
      Met Ile Arg Asn Asp Gln Asp Ser Leu Met Gln Leu Leu Gln Leu Gly  
          1                      5                      10                      15

     Leu Val Val Leu Gly Ser Gln Glu Ser Gln Glu Ser Asp Leu Ser Lys  
                  20                      25                      30

50   Gln Leu Ile Ser Val Ile Ile Gly Leu Gly Val Ala Leu Leu Leu Val  
                  35                      40                      45

     Leu Val Ile Met Thr Met Ala Phe Val Cys Val Arg Lys Ser Tyr Asn  
                  50                      55                      60

55   Arg Lys Leu Gln Ala Met Lys Ala Ala Lys Glu Ala Arg Lys Thr Ala  
          65                      70                      75                      80

60   Ala Gly Val Met Pro Ser Ala Pro Ala Ile Pro Gly Thr Asn Met Tyr  
                          85                      90                      95

Asn Thr Glu Arg Ala Asn Pro Met Leu Asn Leu Pro Asn Lys Asp Leu  
 100 105 110

5 Gly Leu Glu Tyr Leu Ser Pro Ser Asn Asp Leu Asp Ser Val Ser Val  
 115 120 125

Asn Ser Leu Asp Asp Asn Ser Val Asp Val Asp Lys Asn Ser Gln Glu  
 130 135 140

10 Ile Lys Glu His Arg Pro Pro His Thr Pro Pro Glu Pro Asp Pro Glu  
 145 150 155 160

15 Pro Leu Ser Val Val Leu Leu Gly Arg Gln Ala Gly Ala Ser Gly Gln  
 165 170 175

Leu Glu Gly Pro Ser Tyr Thr Asn Ala Gly Leu Asp Thr Thr Asp Leu  
 180 185 190

20 Xaa

25 <210> 111  
 <211> 71  
 <212> PRT  
 <213> Homo sapiens

30 <220>  
 <221> SITE  
 <222> (64)  
 <223> Xaa equals any one of the naturally occurring L-amino acids

35 <400> 111  
 Met Ala His Val Val Val Ala Arg Asn Glu Cys Leu Ile Arg Ala Phe  
 1 5 10 15

Leu Phe Leu Leu His Cys Val Ser Leu Leu Pro Ser Pro Gly Glu Val  
 20 25 30

40 Asn Ile Arg His Thr Leu Phe Thr Val Glu Glu Arg Leu Thr Thr Pro  
 35 40 45

45 Arg Ala Leu Lys Leu Ser Leu Ser Leu Ile Val Ser Leu His Ala Xaa  
 50 55 60

Cys Arg Lys Gln Glu Cys Ser  
 65 70

50 <210> 112  
 <211> 36  
 <212> PRT  
 <213> Homo sapiens

55 <220>  
 <221> SITE  
 <222> (36)  
 <223> Xaa equals stop translation

60

55

<400> 112  
 Met Arg Leu Thr Glu Lys Asp Thr Val Leu Phe Thr Lys Gly Val Leu  
 1 5 10 15  
 5 Phe Leu His Leu Phe Ile Asn Ala Leu Phe Trp Tyr Cys Lys Phe Gly  
 20 25 30  
 His Asn Phe Xaa  
 35  
 10  
 <210> 113  
 <211> 60  
 <212> PRT  
 15 <213> Homo sapiens  
 <220>  
 <221> SITE  
 <222> (60)  
 20 <223> Xaa equals stop translation  
 <400> 113  
 Met Thr Ser Val Ser Thr Gln Leu Ser Leu Val Leu Met Ser Leu Leu  
 1 5 10 15  
 25 Leu Val Leu Pro Val Val Glu Ala Val Glu Ala Gly Asp Ala Ile Ala  
 20 25 30  
 Leu Leu Leu Gly Val Val Leu Ser Ile Thr Gly Ile Cys Ala Cys Leu  
 30 35 40 45  
 Gly Val Tyr Ala Arg Lys Arg Asn Gly Gln Met Xaa  
 50 55 60  
 35  
 <210> 114  
 <211> 29  
 <212> PRT  
 40 <213> Homo sapiens  
 <220>  
 <221> SITE  
 <222> (29)  
 <223> Xaa equals stop translation  
 45  
 <400> 114  
 Met Asn Ser Phe Trp Ser Lys Leu Leu Val Leu Pro Leu Leu Ala Pro  
 1 5 10 15  
 50 Leu Ser Met Ala Arg Ala Ser Ala Cys Gln Arg Trp Xaa  
 20 25  
 55  
 <210> 115  
 <211> 25  
 <212> PRT  
 <213> Homo sapiens  
 <220>  
 60 <221> SITE

&lt;222&gt; (25)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 115

5 Met Met Arg Leu Leu Asp Leu Arg Ile Phe Leu Met Ile His His Lys  
 1 5 10 15

Ala Lys Ser Trp Glu Ser His Thr Xaa  
 20 25

10

&lt;210&gt; 116

&lt;211&gt; 35

&lt;212&gt; PRT

15 &lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (35)

20 &lt;223&gt; Xaa equals stop translation

&lt;400&gt; 116

Met Pro Leu Ser Leu Leu Ile Val Trp Lys Leu Glu Leu Cys Val  
 1 5 10 15

25

Gly Ser Ala Leu Val Leu Ile His Thr Gln Arg Arg Tyr Ile Ile Leu  
 20 25 30

Gln Val Xaa  
 35

30

&lt;210&gt; 117

&lt;211&gt; 78

&lt;212&gt; PRT

35 &lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (78)

40 &lt;223&gt; Xaa equals stop translation

&lt;400&gt; 117

Met Leu Leu Ala Thr Leu Leu Leu Leu Leu Gly Gly Ala Leu Ala  
 1 5 10 15

45

His Pro Asp Arg Ile Ile Phe Pro Asn His Ala Cys Glu Asp Pro Pro  
 20 25 30

50

Ala Val Leu Leu Glu Val Gln Gly Thr Leu Gln Arg Pro Leu Val Arg  
 35 40 45

Asp Ser Arg Thr Ser Pro Ala Asn Cys Thr Trp Leu Thr Lys Arg Val  
 50 55 60

55

Gln Gln Met Leu Leu Phe His Ser Tyr Gly Ile Ala Gln Xaa  
 65 70 75

60 &lt;210&gt; 118

<211> 44  
 <212> PRT  
 <213> Homo sapiens

5 <220>  
 <221> SITE  
 <222> (44)  
 <223> Xaa equals stop translation

10 <400> 118  
 Met Thr Gly Val Phe Lys Leu Pro Leu Leu Phe Trp Val His Glu Ala  
 1 5 10 15  
 Ser Val Gly Gly Cys Pro Tyr Val Lys Leu Val Glu Phe Glu Glu Met  
 15 20 25 30  
 Leu Thr Leu Tyr Gly Ile Leu Leu Ile Leu Phe Xaa  
 35 40

20 <210> 119  
 <211> 46  
 <212> PRT  
 <213> Homo sapiens

25 <220>  
 <221> SITE  
 <222> (46)  
 <223> Xaa equals stop translation

30 <400> 119  
 Met Gln Leu Ala Pro Phe Ile Ser Ile Pro Val Leu Ser Gly Thr Thr  
 1 5 10 15  
 Pro Trp Thr Ala Val Phe Arg Ala Ser Ser Ile Cys Thr Pro Leu Leu  
 35 20 25 30  
 Thr Leu Ser Ala Ala Gly Met Leu Val Glu Ser Ser Leu Xaa  
 40 35 40 45

40 <210> 120  
 <211> 29  
 <212> PRT  
 <213> Homo sapiens

45 <220>  
 <221> SITE  
 <222> (29)  
 <223> Xaa equals stop translation

50 <400> 120  
 Met Pro Pro Leu Ser Asp Ile Leu Leu Thr Val Ala Val Val Ala Phe  
 1 5 10 15  
 Glu Met Thr Gly His Ile Tyr Ile Trp Pro His Thr Xaa  
 55 20 25

60 <210> 121

<211> 62  
 <212> PRT  
 <213> Homo sapiens

5 <400> 121  
 Met Glu Leu Pro Cys Asp Cys Ser Lys Leu Leu Tyr Cys Lys Phe Ser  
 1 5 10 15  
 Val Trp His Leu Pro Val Asn Ala Met Lys Leu Leu Ile Ile Phe Leu  
 10 20 25 30  
 Lys Val Leu His Cys Leu Phe Phe Leu Leu Leu Cys Lys Phe Leu Tyr  
 35 40 45  
 15 Thr Leu Ile Val Ile Leu Thr Asp Lys Tyr Ser Ile Leu Asn  
 50 55 60

20 <210> 122  
 <211> 87  
 <212> PRT  
 <213> Homo sapiens

25 <220>  
 <221> SITE  
 <222> (68)  
 <223> Xaa equals any one of the naturally occurring L-amino acids

30 <220>  
 <221> SITE  
 <222> (72)  
 <223> Xaa equals any one of the naturally occurring L-amino acids

35 <220>  
 <221> SITE  
 <222> (87)  
 <223> Xaa equals stop translation

40 <400> 122  
 Met Pro Val Ser Trp Gly Cys Pro Ser Lys Thr Pro Gln Thr Arg Ala  
 1 5 10 15  
 Tyr Thr Arg Cys Val Tyr Phe Leu Met Val Leu Glu Ala Gly Val Gly  
 20 25 30  
 45 Gly His Ser Val Ser Arg Val Gly Ser Leu Glu Val Pro Pro Trp Leu  
 35 40 45  
 Val Ala Ala Asn Asn Phe Pro His Leu Met Trp Ser Ser Phe Cys Val  
 50 55 60  
 Gly Pro His Xaa Val Phe Leu Xaa Asp Pro Ser Leu Pro Asp Pro Gly  
 65 70 75 80  
 55 Pro Pro Asn Asn Leu Thr Xaa  
 85

60 <210> 123  
 <211> 64



<212> PRT  
 <213> Homo sapiens  
  
 <220>  
 5 <221> SITE  
 <222> (64)  
 <223> Xaa equals stop translation  
  
 <400> 123  
 10 Met Cys Tyr Phe Leu Glu Ile Ser Leu Leu Met Val Phe Ala Leu Asn  
       1                  5                  10                  15  
  
       Ile Lys Ala Ala Tyr Gly Cys Cys Asn Ile Asn Gly Thr Glu Val His  
                   20                  25                  30  
 15 Arg Ala Lys Gly Pro Val Ser Val Pro Phe Pro Leu Ser Arg Pro Leu  
           35                  40                  45  
  
       Ser Gly Thr Pro Leu Leu Asp Arg Leu Arg Pro Phe Gln Thr Leu Xaa  
 20          50                  55                  60  
  
  
 25 <210> 124  
       <211> 36  
       <212> PRT  
       <213> Homo sapiens  
 30 <220>  
       <221> SITE  
       <222> (36)  
       <223> Xaa equals stop translation  
 35 <400> 124  
       Met Pro Leu Pro Ser Ser Phe Pro Leu Pro Val Phe Leu Ser Ser Cys  
           1                  5                  10                  15  
  
 40 Pro Phe Leu Met Ser Val Ser Ile Gly Phe Leu Ile Leu Val Phe Asn  
           20                  25                  30  
  
       Val His Pro Xaa  
           35  
 45 <210> 125  
       <211> 32  
       <212> PRT  
 50 <213> Homo sapiens  
  
       <220>  
       <221> SITE  
       <222> (32)  
 55 <223> Xaa equals stop translation  
  
       <400> 125  
       Met Phe Ile Phe Cys Val Ser Leu Ala Phe Leu Pro Arg Phe Ile Ser  
           1                  5                  10                  15  
 60

Pro Gln Ser Cys Glu Trp Ala Gly Leu Ser Leu Val Trp His His Xaa  
                   20                  25                  30

5

<210> 126

<211> 41

10 <212> PRT

<213> Homo sapiens

<220>

<221> SITE

15 <222> (41)

<223> Xaa equals stop translation

<400> 126

20 Met Lys Asn Asn Thr Gln Lys Arg Leu Phe Leu Trp Gly Glu Leu Leu  
       1                  5                  10                  15

Leu Gln Asp Leu Ala Leu Ile Leu Tyr Leu Ser Ile Phe Leu Lys Ser  
                   20                  25                  30

25 Thr Leu Thr Asn Leu Asn Leu Phe Xaa  
                   35                  40

<210> 127

30 <211> 28

<212> PRT

<213> Homo sapiens

<220>

35 <221> SITE

<222> (28)

<223> Xaa equals stop translation

<400> 127

40 Met Leu Asn Val Phe Phe Ser Leu Ile Leu Phe Phe Ser Pro Asn Arg  
       1                  5                  10                  15

Ala Leu Pro Ala Ile Ser Ser Cys Ile Thr Phe Xaa  
                   20                  25

45

<210> 128

<211> 69

<212> PRT

50 <213> Homo sapiens

<220>

<221> SITE

<222> (69)

55 <223> Xaa equals stop translation

<400> 128

60 Met Arg Ala Val Gly Glu Arg Leu Leu Leu Lys Leu Gln Arg Leu Pro  
       1                  5                  10                  15

Gln Ala Glu Pro Val Glu Ile Val Ala Phe Ser Val Ile Ile Leu Phe  
                   20                  25                  30  
 5 Thr Ala Thr Val Leu Leu Leu Leu Leu Ile Ala Cys Ser Cys Cys Cys  
                   35                  40                  45  
 Thr His Cys Cys Cys Pro Glu Arg Arg Gly Arg Lys Val Gln Val Gln  
           50                  55                  60  
 10 Pro Thr Pro Pro Xaa  
       65  
 15 <210> 129  
       <211> 87  
       <212> PRT  
       <213> Homo sapiens  
       <400> 129  
 20 Met Asp Pro Arg Arg Val Thr Ala Cys Cys His Val Trp Thr Val Gly  
       1                  5                  10                  15  
 Leu Phe Cys Ile Trp Ala Val Gly Leu Ser Cys Ser Leu Ser Leu Ser  
                   20                  25                  30  
 25 His Val Ile Val Trp Leu Ser Gly Ala Gly Cys Thr Leu Ile Cys Glu  
                   35                  40                  45  
 30 Asp Asn Pro Phe Leu Leu Leu Phe Ser Gln Tyr Leu Gln Pro His His  
       50                  55                  60  
 Pro Glu Ile Met Lys Pro Phe Ile Leu Gly His Lys Ser Ser Asn Gly  
       65                  70                  75                  80  
 35 Gly Leu Ser Pro Pro Ser Ala  
                   85  
 40 <210> 130  
       <211> 64  
       <212> PRT  
       <213> Homo sapiens  
       <220>  
 45 <221> SITE  
       <222> (64)  
       <223> Xaa equals stop translation  
       <400> 130  
 50 Met Phe Tyr Met Val Cys Val Leu Gly Ser Gly Ala Gln Pro Leu Ser  
       1                  5                  10                  15  
 Glu Leu Ala Tyr Leu Ala Lys Leu Pro Thr Leu Gln Val Gly Lys Tyr  
                   20                  25                  30  
 55 Asn Pro Leu Phe Asn Lys Ala His Pro Leu His Pro Val Leu Thr Thr  
                   35                  40                  45  
 60 Phe Cys Glu Cys Ala Val Ile Phe Ser Cys Ser Ile Ala Arg Trp Xaa  
       50                  55                  60

5  
 <210> 131  
 <211> 54  
 <212> PRT  
 <213> Homo sapiens

10  
 <400> 131  
 Met Arg Phe Gln Ser Tyr Leu Trp Pro Ser Arg Ile Leu Val Gly Thr  
 1 5 10 15

15  
 Tyr Cys Ile Ala Ala Glu Val Leu Phe Pro Ser Ala Leu Ala Ser Cys  
 20 25 30

Gly Pro Val Trp Gln Gly Gly Ala Pro Thr Lys Ser Trp Gln Pro Gly  
 35 40 45

20  
 Ala Lys Thr Ile Ile Pro  
 50

25  
 <210> 132  
 <211> 41  
 <212> PRT  
 <213> Homo sapiens

30  
 <220>  
 <221> SITE  
 <222> (41)  
 <223> Xaa equals stop translation

35  
 <400> 132  
 Met Arg Arg Trp Ala Gly Phe Gly Lys Ser Pro Gln Phe Trp Trp Thr  
 1 5 10 15

40  
 Gly Ile Leu Val Ala Leu Gly Ala Ala Leu Leu Gly Gly Pro Arg Leu  
 20 25 30

Gly Arg Arg Leu Thr Phe Gly Leu Xaa  
 35 40

45  
 <210> 133  
 <211> 69  
 <212> PRT  
 <213> Homo sapiens

50  
 <220>  
 <221> SITE  
 <222> (69)  
 <223> Xaa equals stop translation

55  
 <400> 133  
 Met Ala Leu Ala Ile Phe Ile Pro Val Leu Ile Ile Ser Leu Leu Leu  
 1 5 10 15

60  
 Gly Gly Ala Tyr Ile Tyr Ile Thr Arg Cys Arg Tyr Tyr Ser Asn Leu

20 25 30  
 Arg Leu Pro Leu Met Tyr Ser His Pro Tyr Ser Gln Ile Thr Val Glu  
 35 40 45  
 5 Thr Glu Phe Asp Asn Pro Ile Tyr Glu Thr Gly Glu Thr Arg Glu Tyr  
 50 55 60  
 Glu Val Ser Ile Xaa  
 10 65  
 <210> 134  
 <211> 48  
 15 <212> PRT  
 <213> Homo sapiens  
 <220>  
 <221> SITE  
 20 <222> (48)  
 <223> Xaa equals stop translation  
 <400> 134  
 25 Met Gly Phe Leu Phe Leu His Ile Leu Pro Ser Ile Ile Asn Thr Arg  
 1 5 10 15  
 Ser Ala Pro Gln Pro Thr Ser Cys Arg Met Gln Pro Glu Gln Gln Pro  
 20 25 30  
 30 His Ser Thr Leu Lys Pro Val Ile Leu Gly Met Met Ile Ile Ser Xaa  
 35 40 45  
 35  
 <210> 135  
 <211> 76  
 <212> PRT  
 40 <213> Homo sapiens  
 <400> 135  
 Met Ser Gly Leu Val Gly Gly Gly Ser Arg Cys Ser Lys Val Arg Phe  
 1 5 10 15  
 45 Arg Cys Phe Asn Gly Asp Ser Leu Leu Val Leu Val Leu Gln His His  
 20 25 30  
 Phe Arg Leu Cys Ser Trp Cys Leu Ala Pro Ser Leu Phe Leu Leu Leu  
 50 35 40 45  
 Ser Cys Gln Val Val Ser Thr Met Met Glu Gln Asp Pro Val Ile Tyr  
 50 55 60  
 55 Asp Asp Asp Asp Asp Leu Pro Asn Tyr Phe Ser Val  
 65 70 75  
 60 <210> 136  
 <211> 55

<212> PRT  
 <213> Homo sapiens

5 <220>  
 <221> SITE  
 <222> (32)  
 <223> Xaa equals any one of the naturally occurring L-amino acids

10 <220>  
 <221> SITE  
 <222> (39)  
 <223> Xaa equals any one of the naturally occurring L-amino acids

15 <220>  
 <221> SITE  
 <222> (55)  
 <223> Xaa equals stop translation

20 <400> 136  
 Met Phe Leu Glu Leu Pro Met Gln His Ser Asp Val Leu Leu Phe Leu  
           1                  5                  10                  15

Val Cys Trp Lys Ala Met Gly Ser Lys Lys Ser Pro Ser His Phe Xaa  
                   20                  25                  30

25 Pro Glu Val Gly Gly Ile Xaa Pro Ser Phe Gly Met Leu Asn Val Thr  
                   35                  40                  45

30 Leu Leu Arg Ser Leu Thr Xaa  
           50                  55

35 <210> 137  
 <211> 54  
 <212> PRT  
 <213> Homo sapiens

40 <400> 137  
 Met Leu Val Leu Phe Pro Leu Leu Tyr Arg Gly Trp Ser Pro Val Pro  
           1                  5                  10                  15

Gly Thr Ala Glu Gly Gly Met Cys Cys Cys Cys Leu Cys Ile Ser Arg  
                   20                  25                  30

45 Tyr Ser Leu Leu Thr Ser Ser Gln Asp Lys Glu Pro Pro Tyr Glu Met  
                   35                  40                  45

Ser Ser Ser Glu Leu Ser  
           50

50 <210> 138  
 <211> 36  
 <212> PRT  
 55 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (33)  
 60 <223> Xaa equals any one of the naturally occurring L-amino acids

65

<220>  
 <221> SITE  
 <222> (36)  
 5 <223> Xaa equals stop translation

<400> 138  
 Met Thr Cys Tyr Glu Val Ile Leu Phe Phe Ile Lys Leu Phe Ser Asp  
 1 5 10 15  
 10 Met Gly Lys Tyr Lys Glu Cys Lys Glu Phe Lys Lys Gln Arg Thr Lys  
 20 25 30  
 15 Xaa Tyr Met Xaa  
 35

<210> 139  
 <211> 80  
 20 <212> PRT  
 <213> Homo sapiens

<400> 139  
 Met Lys Ala Gln Pro Leu Glu Ala Leu Leu Leu Val Ala Leu Val Leu  
 1 5 10 15  
 Ser Phe Cys Gly Val Trp Phe Glu Asp Trp Leu Ser Lys Trp Arg Phe  
 20 25 30  
 30 Gln Cys Ile Phe Gln Leu Ala His Gln Pro Ala Leu Val Asn Ile Gln  
 35 40 45  
 Phe Arg Gly Thr Val Leu Gly Ser Glu Thr Phe Leu Gly Ala Glu Glu  
 50 55 60  
 35 Asn Ser Ala Asp Val Arg Ser Trp Gln Thr Leu Ser Tyr Phe Glu Leu  
 65 70 75 80

40

<210> 140  
 <211> 67  
 45 <212> PRT  
 <213> Homo sapiens

<400> 140  
 Met Ala Ala Ser Val Gly Arg Ala Thr Arg Ser Ala Ala Ala His Leu  
 1 5 10 15  
 Thr Gln Leu Pro Pro Ala Pro Arg Ala Gln Arg Thr Ser Pro Ala Gln  
 20 25 30  
 55 Pro Asp Glu Gly Lys Arg Arg Asp Ala Asp Pro Trp Arg Thr Gly Pro  
 35 40 45  
 Thr Val Asn Lys Thr Gly Ser Ile Pro Gly Arg Leu Arg Gly Trp Ala  
 50 55 60

60

Arg Ala Glu  
65

5 <210> 141  
<211> 51  
<212> PRT  
<213> Homo sapiens

10 <220>  
<221> SITE  
<222> (51)  
<223> Xaa equals stop translation

15 <400> 141  
Met Gly Trp Leu Cys Cys Glu Pro Ser Gly Leu Tyr Asn Leu Glu Lys  
1 5 10 15

20 Gln Tyr Phe Phe Phe Ser Ser Leu Gln Ala Gly Leu Pro Val Ile Val  
20 25 30

Ser Ser Gly Cys Thr Lys Ile Ala Tyr Gly Phe Ala Val Tyr Ser Pro  
35 40 45

25 Ser Ser Xaa  
50

30 <210> 142  
<211> 54  
<212> PRT  
<213> Homo sapiens

<400> 142  
35 Met Arg Arg Cys Val Arg His Val Leu Gly Ile Gly Leu Ile Val Leu  
1 5 10 15

Lys Asn Leu Tyr Phe His Lys Asn Ser Met Tyr Pro Ser Pro Lys Leu  
20 25 30

40 Ser Ser Phe Gln Glu Ala Phe Leu Phe Phe Phe Leu Ile Leu Lys Asn  
35 40 45

45 Pro Leu Thr Leu Cys Ser  
50

50 <210> 143  
<211> 50  
<212> PRT  
<213> Homo sapiens

<220>  
<221> SITE  
55 <222> (50)  
<223> Xaa equals stop translation

<400> 143  
60 Ile His Pro Ser Arg Ser Thr Leu Ser Ser Gln Leu Val Thr Leu Pro  
1 5 10 15



Leu Phe Glu Leu Val Phe Pro Ile Pro Ser Ser Gln Ser Pro Phe Ser  
                   20                  25                  30

5 Leu Asn Tyr Leu Ser Glu Phe Pro Leu Pro Glu His Glu Pro Cys Leu  
                   35                  40                  45

Glu Xaa  
       50

10

<210> 144  
 <211> 87  
 <212> PRT  
 15 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (84)  
 20 <223> Xaa equals any one of the naturally occurring L-amino acids

<220>  
 <221> SITE  
 <222> (87)  
 25 <223> Xaa equals stop translation

<400> 144  
 Met Thr Cys Cys Cys Leu Leu Cys Lys Leu Gln Gly Ile Phe Phe Phe  
       1                  5                  10                  15

30 Ser Phe Asn Ser Ser Val Leu Lys Ser Ile Leu Gly Thr Thr Arg Thr  
                   20                  25                  30

Leu Ser Ala Pro Trp Ile Gly Val Ser Val Lys Gly Thr Gln Trp Ala  
       35                  40                  45

35 Leu Gly Ser Ala Arg Pro Gly Cys Gly Ser Gln Leu Thr Ser Ser Leu  
       50                  55                  60

40 Gly Gly Leu Arg Gln Val Ile Cys Gln Pro His Leu Gln Lys His Asp  
       65                  70                  75                  80

Ala Lys Leu Xaa Ser Val Xaa  
                   85

45

<210> 145  
 <211> 57  
 <212> PRT  
 50 <213> Homo sapiens

<400> 145  
 Met His Lys Cys Asn Thr Val Thr Arg Glu Leu Leu Gln Leu Ser Leu  
       1                  5                  10                  15

55 Leu Ile Leu Pro Ser Gln Cys Gly Asn Cys Ala Thr Ser Thr Lys Arg  
                   20                  25                  30

Gly Pro Arg Leu Leu Lys Tyr Phe Arg Thr Ser Pro Gln Glu Gln Thr  
       35                  40                  45

60

Pro Leu His Leu Asp Ser Asp Cys Ser  
50 55

5

<210> 146  
<211> 87  
<212> PRT  
<213> Homo sapiens

10

<400> 146  
Met Ser His Cys Ala Arg Pro Leu Phe Phe Glu Thr Phe Phe Ile Leu  
1 5 10 15

15

Leu Ser Pro Arg Leu Lys Cys Ser Gly Thr Asn Thr Val His Tyr Ser  
20 25 30

Leu Asp Leu Leu Gly Ser Ser Asn Ser Ala Ser Val Pro Gln Val Gly  
35 40 45

20

Gly Leu Thr Asn Ala Gln His Asp Thr Trp Leu Ile Phe Val Phe Cys  
50 55 60

25

Val Cys Val Cys Glu Pro Leu Arg Arg Pro Trp Ala Ala Phe Leu Ile  
65 70 75 80

Ser Val Thr Ser Ser Ile Lys  
85

30

<210> 147  
<211> 230  
<212> PRT  
<213> Homo sapiens

35

<220>  
<221> SITE  
<222> (216)  
<223> Xaa equals any one of the naturally occurring L-amino acids

40

<400> 147  
Met Gly Leu Ala Leu Tyr Val Leu Pro Val Leu Gly Gln His Val Ala  
1 5 10 15

45

Thr Gln His Phe Pro Val Ala Glu Ala Glu Ala Val Val Leu Thr Leu  
20 25 30

Leu Ala Ile Tyr Ala Ala Gly Leu Ala Leu Pro His Asn Thr His Arg  
35 40 45

50

Val Val Ser Thr Gln Ala Pro Asp Arg Gly Trp Met Ala Leu Lys Leu  
50 55 60

55

Val Ala Leu Ile Tyr Leu Ala Leu Gln Leu Gly Cys Ile Ala Leu Thr  
65 70 75 80

Asn Phe Ser Leu Gly Phe Leu Leu Ala Thr Thr Met Val Pro Thr Ala  
85 90 95

60

Ala Leu Ala Lys Pro His Gly Pro Arg Thr Leu Tyr Ala Ala Leu Leu

100 105 110  
 Val Leu Thr Ser Pro Ala Ala Thr Leu Leu Gly Ser Leu Phe Leu Trp  
 115 120 125  
 5 Arg Glu Leu Gln Glu Ala Pro Leu Ser Leu Ala Glu Gly Trp Gln Leu  
 130 135 140  
 Phe Leu Ala Ala Leu Ala Gln Gly Val Leu Glu His His Thr Thr Ala  
 10 145 150 155 160  
 Pro Cys Ser Ser His Cys Cys Pro Trp Ala Ser Thr Pro Ala Gly Cys  
 165 170 175  
 15 Phe Ser Gly Met Cys Ser Ser Gly Ser Glu Ile Cys Leu Ser Gly Leu  
 180 185 190  
 Gly Gln Arg Leu Pro Lys Asp Pro Ile Leu Pro Pro Ser Gly Glu Ile  
 195 200 205  
 20 Asn Glu Cys Leu Phe Gln Gln Xaa Lys Lys Lys Lys Lys Lys Lys Lys  
 210 215 220  
 Lys Lys Lys Lys Gly Gly  
 25 225 230  
 <210> 148  
 <211> 63  
 30 <212> PRT  
 <213> Homo sapiens  
 <220>  
 <221> SITE  
 35 <222> (63)  
 <223> Xaa equals stop translation  
 <400> 148  
 Gln Pro Ala Leu Leu Tyr Leu Val Pro Ala Cys Ile Gly Phe Pro Val  
 40 1 5 10 15  
 Leu Val Ala Leu Ala Lys Gly Glu Val Thr Glu Met Phe Ser Tyr Glu  
 20 25 30  
 45 Glu Ser Asn Pro Lys Asp Pro Ala Ala Val Thr Glu Ser Lys Glu Gly  
 35 40 45  
 Thr Glu Ala Ser Ala Ser Lys Gly Leu Glu Lys Lys Glu Lys Xaa  
 50 50 55 60  
 <210> 149  
 <211> 18  
 <212> PRT  
 55 <213> Homo sapiens  
 <220>  
 <221> SITE  
 <222> (18)  
 60 <223> Xaa equals stop translation

&lt;400&gt; 149

Gln Leu Ile Leu Ser Leu Leu Arg Gly Phe Cys Lys Thr Glu Arg Val  
1 5 10 15

5

Gly Xaa

10

&lt;210&gt; 150

&lt;211&gt; 16

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

15

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (16)

&lt;223&gt; Xaa equals stop translation

20

&lt;400&gt; 150

Met Ala Leu Gly Ala Arg Glu Leu Pro Gly Ser Leu Ser Arg Trp Xaa  
1 5 10 15

25

&lt;210&gt; 151

&lt;211&gt; 22

30

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

35

&lt;222&gt; (22)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 151

Met Tyr Ser Phe Ser Val Leu Glu Ile Thr Cys Phe Ile Leu Phe Leu  
1 5 10 15

40

Trp Pro Ser Trp Val Xaa  
20

45

&lt;210&gt; 152

&lt;211&gt; 25

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

50

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (25)

&lt;223&gt; Xaa equals stop translation

55

&lt;400&gt; 152

Met Lys Ile Lys Gln Arg Phe Ser Leu Leu Leu Phe His Cys Pro Phe  
1 5 10 15

60

Pro Pro Cys Cys Leu Ser Leu Gly Xaa

20 25

5 <210> 153  
 <211> 40  
 <212> PRT  
 <213> Homo sapiens

10 <400> 153  
 Met Asn Gly Leu Phe Gln Leu Glu Ile Ser His Lys Leu Trp Thr Lys  
 1 5 10 15

Ser Lys Thr Ser Leu Met Thr Leu Leu Ser Val Met Ala Leu Leu Trp  
 20 25 30

15 Lys Ile Leu Trp Ser Arg Ala Ile  
 35 40

20 <210> 154  
 <211> 25  
 <212> PRT  
 <213> Homo sapiens

25 <220>  
 <221> SITE  
 <222> (25)  
 <223> Xaa equals stop translation

30 <400> 154  
 Met Thr Pro Gly Leu Phe Leu Tyr Phe Val Cys Val Cys Val Ser His  
 1 5 10 15

35 Cys Ala Gly Leu Gly Gln Leu Ser Xaa  
 20 25

40 <210> 155  
 <211> 103  
 <212> PRT  
 <213> Homo sapiens

45 <400> 155  
 Ile Arg His Glu Leu Gly Cys Ser Trp Arg Phe Arg Ala Val Lys Ala  
 1 5 10 15

Ala Ser Ala Gln Gly Leu Phe Leu Ser Ala Pro Gly Pro Ala Ala Arg  
 20 25 30

50 Arg Cys His Gly Val Val Arg Cys Phe Ser Thr Cys Arg Ala Leu Thr  
 35 40 45

Ala Arg Cys Thr Gly Arg Val Pro Trp Glu Ala Cys Leu Tyr Ser Ser  
 50 55 60

55 Glu Pro Pro Leu Thr Glu Thr Val Ala Arg Ser Val Ser Trp Thr Cys  
 65 70 75 80

60 Glu Leu Ala Leu Thr Cys Tyr Ala Pro Arg Ala Leu Ser Gly Ala Pro  
 85 90 95

Val Leu Cys Arg His Asp Val  
100

5

<210> 156  
<211> 46  
<212> PRT  
<213> Homo sapiens

10

<400> 156  
Phe Leu Ala Ile His Phe Pro Thr Asp Phe Pro Leu Lys Pro Pro Lys  
1 5 10 15

15

Val Ala Phe Thr Arg Met Tyr Phe Pro Asn Ser Asn Ser Asn Gly Ser  
20 25 30

Thr Cys Leu Asp Ile Leu Trp Ser Gln Trp Ser Pro Ala Leu  
35 40 45

20

<210> 157  
<211> 101  
<212> PRT

25

<213> Homo sapiens

<400> 157  
Met Leu Leu Thr Pro His Phe Asn Val Ala Asn Pro Gln Asn Leu Leu  
1 5 10 15

30

Ala Gly Leu Trp Leu Glu Asn Glu His Ser Phe Thr Leu Met Ala Pro  
20 25 30

35

Glu Arg Ala Arg Thr His His Cys Gln Pro Glu Glu Arg Lys Val Leu  
35 40 45

Phe Cys Leu Phe Pro Ile Val Pro Asn Ser Gln Ala Gln Val Gln Pro  
50 55 60

40

Pro Gln Met Pro Pro Phe Cys Cys Ala Ala Ala Lys Glu Lys Thr Gln  
65 70 75 80

Glu Glu Gln Leu Gln Glu Pro Leu Gly Ser Gln Cys Pro Asp Thr Cys  
85 90 95

45

Pro Asn Ser Leu Cys  
100

50

<210> 158  
<211> 211  
<212> PRT  
<213> Homo sapiens

55

<400> 158  
Met Arg Leu Phe Leu Trp Asn Ala Val Leu Thr Leu Phe Val Thr Ser  
1 5 10 15

60

Leu Ile Gly Ala Leu Ile Pro Glu Pro Glu Val Lys Ile Glu Val Leu  
20 25 30

Gln Lys Pro Phe Ile Cys His Arg Lys Thr Lys Gly Gly Asp Leu Met  
                   35                                  40                                  45

5   Leu Val His Tyr Glu Gly Tyr Leu Glu Lys Asp Gly Ser Leu Phe His  
           50                                  55                                  60

Ser Thr His Lys His Asn Asn Gly Gln Pro Ile Trp Phe Thr Leu Gly  
   65                                  70                                  75                                  80

10   Ile Leu Glu Ala Leu Lys Gly Trp Asp Gln Gly Leu Lys Gly Met Cys  
                                   85                                  90                                  95

15   Val Gly Glu Lys Arg Lys Leu Ile Ile Pro Pro Ala Leu Gly Tyr Gly  
                                   100                                  105                                  110

Lys Glu Gly Lys Gly Lys Ile Pro Pro Glu Ser Thr Leu Ile Phe Asn  
           115                                  120                                  125

20   Ile Asp Leu Leu Glu Ile Arg Asn Gly Pro Arg Ser His Glu Ser Phe  
           130                                  135                                  140

Gln Glu Met Asp Leu Asn Asp Asp Trp Lys Leu Ser Lys Asp Glu Val  
   145                                  150                                  155                                  160

25   Lys Ala Tyr Leu Lys Lys Glu Phe Glu Lys His Gly Ala Val Val Asn  
                                   165                                  170                                  175

Glu Ser His His Asp Ala Leu Val Glu Asp Ile Phe Asp Lys Glu Asp  
                                   180                                  185                                  190

30   Glu Asp Lys Asp Gly Phe Ile Ser Ala Arg Glu Phe Thr Tyr Lys His  
           195                                  200                                  205

35   Asp Glu Leu  
           210

40   <210> 159  
       <211> 186  
       <212> PRT  
       <213> Homo sapiens

45   <400> 159  
       Glu Val Lys Ile Glu Val Leu Gln Lys Pro Phe Ile Cys His Arg Lys  
           1                                  5                                  10                                  15

Thr Lys Gly Gly Asp Leu Met Leu Val His Tyr Glu Gly Tyr Leu Glu  
                                   20                                  25                                  30

50   Lys Asp Gly Ser Leu Phe His Ser Thr His Lys His Asn Asn Gly Gln  
           35                                  40                                  45

Pro Ile Trp Phe Thr Leu Gly Ile Leu Glu Ala Leu Lys Gly Trp Asp  
   55           50                                  55                                  60

Gln Gly Leu Lys Gly Met Cys Val Gly Glu Lys Arg Lys Leu Ile Ile  
   65                                   70                                  75                                  80

60   Pro Pro Ala Leu Gly Tyr Gly Lys Glu Gly Lys Lys Ile Pro Pro

74

	85	90	95	
	Glu Ser Thr Leu Ile Phe Asn Ile Asp Leu Leu Glu Ile Arg Asn Gly			
	100	105	110	
5	Pro Arg Ser His Glu Ser Phe Gln Glu Met Asp Leu Asn Asp Asp Trp			
	115	120	125	
10	Lys Leu Ser Lys Asp Glu Val Lys Ala Tyr Leu Lys Lys Glu Phe Glu			
	130	135	140	
	Lys His Gly Ala Val Val Asn Glu Ser His His Asp Ala Leu Val Glu			
	145	150	155	160
15	Asp Ile Phe Asp Lys Glu Asp Glu Asp Lys Asp Gly Phe Ile Ser Ala			
	165	170	175	
20	Arg Glu Phe Thr Tyr Lys His Asp Glu Leu			
	180	185		
	<210> 160			
	<211> 633			
	<212> DNA			
25	<213> Homo sapiens			
	<400> 160			
	ATGAGGCTTT TCTGTGGAA CGCGGTCTTG ACTCTGTTTG TCACTTCTTT GATTGGGGCT	60		
30	TTGATCCCTG AACCAGAAGT GAAAATTGAA GTTCTCCAGA AGCCATTCAT CTGCCATCGC	120		
	AAGACCAAAG GAGGGGATTT GATGTTGGTC CACTATGAAG GCTACTTAGA AAAGGACGGC	180		
35	TCCTTATTTT ACTCCACTCA CAAACATAAC AATGGTCAGC CCATTTGGTT TACCCTGGGC	240		
	ATCCTGGAGG CTCTCAAAGG TTGGGACCAG GGCTTGAAAG GAATGTGTGT AGGAGAGAAG	300		
	AGAAAGCTCA TCATTCTCTC TGCTCTGGGC TATGGAAAAG AAGGAAAAGG TAAAATTCCC	360		
40	CCAGAAAGTA CACTGATATT TAATATTGAT CTCTGGAGA TTCGAAATGG ACCAAGATCC	420		
	CATGAATCAT TCCAAGAAAT GGATCTTAAT GATGACTGGA AACTCTCTAA AGATGAGGTT	480		
45	AAAGCATATT TAAAGAAGGA GTTTGAAAAA CATGGTGCGG TGGTGAATGA AAGTCATCAT	540		
	GATGCTTTGG TGGAGGATAT TTTTGATAAA GAAGATGAAG ACAAAGATGG GTTTATATCT	600		
	GCCAGAGAAT TTACATATAA ACACGATGAG TTA	633		
50				
	<210> 161			
	<211> 22			
	<212> PRT			
55	<213> Homo sapiens			
	<400> 161			
	Leu Arg Ser Val Val Gln Asp His Pro Gly Gln His Gly Glu Thr Pro			
60	1 5 10 15			



Ser Leu Leu Lys Ile Gln  
20

- 5 <210> 162  
<211> 57  
<212> PRT  
<213> Homo sapiens
- 10 <220>  
<221> SITE  
<222> (34)  
<223> Xaa equals any one of the naturally occurring L-amino acids
- 15 <400> 162  
Met Phe Tyr Asn Phe Val Arg Gln Leu Asp Thr Val Ser Ile Glu His  
1 5 10 15
- 20 Ala Gly Lys Ser Lys Leu Lys Met Thr Val Gly Thr Lys Leu Thr Ser  
20 25 30
- Gly Xaa Gly Pro Arg Lys Ser Ser Gln Ser Gly Arg Ile Ala Ala Ser  
35 40 45
- 25 Ile Thr Asp Cys Gln Gln Cys Lys Ala  
50 55
- 30 <210> 163  
<211> 46  
<212> PRT  
<213> Homo sapiens
- 35 <220>  
<221> SITE  
<222> (16)  
<223> Xaa equals any one of the naturally occurring L-amino acids
- 40 <400> 163  
Met Glu Ala Ala Ile Leu Pro Leu Trp Leu Leu Phe Leu Gly Pro Xaa  
1 5 10 15
- Pro Glu Val Ser Phe Val Pro Thr Val Ile Phe Asn Leu Asp Phe Pro  
20 25 30
- 45 Ala Cys Ser Ile Leu Thr Val Ser Ser Cys Leu Thr Lys Leu  
35 40 45
- 50 <210> 164  
<211> 25  
<212> PRT  
<213> Homo sapiens
- 55 <400> 164  
Asn His Gly His Ser Cys Phe Leu Cys Glu Ile Val Ile Arg Ser Gln  
1 5 10 15
- 60 Phe His Thr Thr Tyr Glu Pro Glu Ala  
20 25

5 <210> 165  
 <211> 48  
 <212> PRT  
 <213> Homo sapiens  
  
 <400> 165  
 10 Ser Gly Arg His Arg Val Glu Leu Gln Leu Leu Phe Pro Leu Val Arg  
     1                    5                    10                    15  
 Val Asn Phe Glu Leu Gly Val Asn His Gly His Ser Cys Phe Leu Cys  
             20                    25                    30  
 15 Glu Ile Val Ile Arg Ser Gln Phe His Thr Thr Tyr Glu Pro Glu Ala  
             35                    40                    45  
  
 20  
  
 <210> 166  
 <211> 141  
 <212> PRT  
 25 <213> Homo sapiens  
  
 <400> 166  
 30 Met Asn Ala Arg Gly Leu Gly Ser Glu Leu Lys Asp Ser Ile Pro Val  
     1                    5                    10                    15  
 Thr Glu Leu Ser Ala Ser Gly Pro Phe Glu Ser His Asp Leu Leu Arg  
             20                    25                    30  
 Lys Gly Phe Ser Cys Val Lys Asn Glu Leu Leu Pro Ser His Pro Leu  
 35              35                    40                    45  
 Glu Leu Ser Glu Lys Asn Phe Gln Leu Asn Gln Asp Lys Met Asn Phe  
     50                    55                    60  
 40 Ser Thr Leu Arg Asn Ile Gln Gly Leu Phe Ala Pro Leu Lys Leu Gln  
     65                    70                    75                    80  
 Met Glu Phe Lys Ala Val Gln Gln Val Gln Arg Leu Pro Phe Leu Ser  
             85                    90                    95  
 45 Ser Ser Asn Leu Ser Leu Asp Val Leu Arg Gly Asn Asp Glu Thr Ile  
             100                    105                    110  
 Gly Phe Glu Asp Ile Leu Asn Asp Pro Ser Gln Ser Glu Val Met Gly  
 50              115                    120                    125  
 Glu Pro His Leu Met Val Glu Tyr Lys Leu Gly Leu Leu  
     130                    135                    140  
  
 55 <210> 167  
 <211> 15  
 <212> PRT  
 60 <213> Homo sapiens

<400> 167  
 Gly Gly Asn Lys Tyr Gln Thr Ile Asp Asn Tyr Gln Pro Tyr Pro  
 1 5 10 15

5

<210> 168  
 <211> 20  
 <212> PRT  
 <213> Homo sapiens

10

<400> 168  
 Pro Leu Leu Gly Val Ser Ala Thr Leu Asn Ser Val Leu Asn Ser Asn  
 1 5 10 15

15

Ala Ile Lys Asn  
 20

20

<210> 169  
 <211> 14  
 <212> PRT  
 <213> Homo sapiens

25

<400> 169  
 Gly Ser Ala Val Ser Ala Ala Pro Gly Ile Leu Tyr Pro Gly  
 1 5 10

30

<210> 170  
 <211> 81  
 <212> PRT  
 <213> Homo sapiens

35

<400> 170  
 Ala Gly Ile Gln His Glu Leu Ala Cys Asp Asn Pro Gly Leu Pro Glu  
 1 5 10 15

40

Asn Gly Tyr Gln Ile Leu Tyr Lys Arg Leu Tyr Leu Pro Gly Glu Ser  
 20 25 30

Leu Thr Phe Met Cys Tyr Glu Gly Phe Glu Leu Met Gly Glu Val Thr  
 35 40 45

45

Ile Arg Cys Ile Leu Gly Gln Pro Ser His Trp Asn Gly Pro Leu Pro  
 50 55 60

Val Cys Lys Val Ala Glu Ala Ala Ala Glu Thr Ser Leu Glu Gly Gly  
 65 70 75 80

50

Asn

55

<210> 171  
 <211> 27  
 <212> PRT  
 <213> Homo sapiens

60

<400> 171  
 Gln Pro Ser His Trp Asn Gly Pro Leu Pro Val Cys Lys Val Ala Glu

1                      5                      10                      15  
 Ala Ala Ala Glu Thr Ser Leu Glu Gly Gly Asn  
                     20                      25  
 5  
 <210> 172  
 <211> 13  
 <212> PRT  
 10 <213> Homo sapiens  
 <400> 172  
 Tyr Glu Thr Gly Glu Thr Arg Glu Tyr Glu Val Ser Ile  
       1                      5                      10  
 15  
 <210> 173  
 <211> 195  
 <212> PRT  
 20 <213> Homo sapiens  
 <220>  
 <221> SITE  
 <222> (40)  
 25 <223> Xaa equals any one of the naturally occurring L-amino acids  
 <220>  
 <221> SITE  
 <222> (161)  
 30 <223> Xaa equals any one of the naturally occurring L-amino acids  
 <400> 173  
 Asp Asp Asp Gly Leu Pro Phe Pro Thr Asp Val Ile Gln His Arg Leu  
       1                      5                      10                      15  
 35  
 Arg Gln Ile Glu Ala Gly Tyr Lys Gln Glu Val Glu Gln Leu Arg Arg  
                     20                      25                      30  
 Gln Val Arg Asp Ser Asp Glu Xaa Gly His Pro Ser Leu Leu Cys Pro  
 40                      35                      40                      45  
 Ser Ser Arg Ala Pro Met Asp Tyr Glu Asp Asp Phe Thr Cys Leu Lys  
       50                      55                      60  
 45  
 Glu Ser Asp Gly Ser Asp Thr Glu Asp Phe Gly Ser Asp His Ser Glu  
       65                      70                      75                      80  
 Asp Cys Leu Ser Glu Ala Ser Trp Glu Pro Val Asp Lys Lys Glu Thr  
                     85                      90                      95  
 50  
 Glu Val Thr Arg Trp Val Pro Asp His Met Ala Ser His Cys Tyr Asn  
                     100                      105                      110  
 Cys Asp Cys Glu Phe Trp Leu Ala Lys Arg Arg His His Cys Arg Asn  
 55                      115                      120                      125  
 Cys Gly Asn Val Phe Cys Ala Gly Cys Cys His Leu Lys Leu Pro Ile  
       130                      135                      140  
 60 Pro Asp Gln Gln Leu Tyr Asp Pro Val Leu Val Cys Asn Ser Cys Tyr

145                      150                      155                      160  
 Xaa Thr His Ser Ser Leu Ser Cys Gln Gly Thr His Glu Pro Thr Ala  
                                  165                      170                      175  
 5      Glu Glu Thr His Cys Tyr Ser Phe Gln Leu Asn Ala Gly Glu Lys Pro  
                                  180                      185                      190  
 10      Val Gln Phe  
                                  195  
 <210> 174  
 <211> 28  
 15      <212> PRT  
             <213> Homo sapiens  
 <400> 174  
 Ser Glu Ala Ser Trp Glu Pro Val Asp Lys Lys Glu Thr Glu Val Thr  
 20      1                      5                      10                      15  
 Arg Trp Val Pro Asp His Met Ala Ser His Cys Tyr  
                                  20                      25  
 25      <210> 175  
             <211> 10  
             <212> PRT  
             <213> Homo sapiens  
 30      <400> 175  
 His His Cys Arg Asn Cys Gly Asn Val Phe  
             1                      5                      10  
 35      <210> 176  
             <211> 14  
             <212> PRT  
             <213> Homo sapiens  
 40      <400> 176  
 Arg Leu Arg Gln Ile Glu Ala Gly Tyr Lys Gln Glu Val Glu  
             1                      5                      10  
 45      <210> 177  
             <211> 87  
             <212> PRT  
             <213> Homo sapiens  
 50      <400> 177  
 Met Ser His Cys Ala Arg Pro Leu Phe Phe Glu Thr Phe Phe Ile Leu  
             1                      5                      10                      15  
 55      Leu Ser Pro Arg Leu Lys Cys Ser Gly Thr Asn Thr Val His Tyr Ser  
                                  20                      25                      30  
 Leu Asp Leu Leu Gly Ser Ser Asn Ser Ala Ser Val Pro Gln Val Gly  
             35                      40                      45  
 60

80

Gly Leu Thr Asn Ala Gln His Asp Thr Trp Leu Ile Phe Val Phe Cys  
50 55 60

5 Val Cys Val Cys Glu Pro Leu Arg Arg Pro Trp Ala Ala Phe Leu Ile  
65 70 75 80

Ser Val Thr Ser Ser Ile Lys  
85

10

&lt;210&gt; 178

&lt;211&gt; 30

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

15

&lt;400&gt; 178

Val Pro Gln Val Gly Gly Leu Thr Asn Ala Gln His Asp Thr Trp Leu  
1 5 10 15

20 Ile Phe Val Phe Cys Val Cys Val Cys Glu Pro Leu Arg Arg  
20 25 30